

Barb

Access DB# 97458

# SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: P. SWINACK Examiner #: 76400 Date: 6/16/95  
Art Unit: 1614 Phone Number 301 89703 Serial Number: 11621/77  
Mail Box and Bldg/Room Location: 2D01 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

\*\*\*\*\*  
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Modulation Stimulation Inhibition Glutamate Receptor  
Inventors (please provide full names): Maria-Luisa Marrero  
Pei Xue-Feng Shuichi Tawara  
Earliest Priority Filing Date: 10/30/90

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search  
methods of treating a disease involving glutamate levels  
or  
modulating, stimulating & inhibiting  
glutamate receptors.

comprising administer SYM 2081  
SYM 2183  
SYM 2062  
SYM 2051

each

THANK

## STAFF USE ONLY

	Type of Search	Vendors and cost where applicable
Searcher: <u>SWP</u>	NA Sequence (#) _____	STN _____
Searcher Phone #: _____	AA Sequence (#) _____	Dialog _____
Searcher Location: _____	Structure (#) _____	Questel/Orbit _____
Date Searcher Picked Up: _____	Bibliographic <u>X</u>	Dr.Link _____
Date Completed: <u>6-25-95</u>	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: <u>15</u>	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time: <u>21</u>	Other _____	Other (specify) _____

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=> fil reg; d ide l10; d ide l11; d ide l12; d ide l13  
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 24 JUN 2003 HIGHEST RN 536971-45-6  
DICTIONARY FILE UPDATES: 24 JUN 2003 HIGHEST RN 536971-45-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

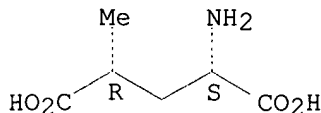
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

*Registry  
records for  
4 compounds*

L10 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS  
RN 31137-74-3 REGISTRY  
CN L-Glutamic acid, 4-methyl-, (4R)- (9CI) (CA INDEX NAME)  
OTHER CA INDEX NAMES:  
CN Glutamic acid, 4-methyl-, L-erythro- (8CI)  
CN L-Glutamic acid, 4-methyl-, erythro-  
OTHER NAMES:  
CN (2S,4R)-4-Methylglutamic acid  
CN erythro-.gamma.-Methyl-L-glutamic acid  
CN erythro-.gamma.-Methylglutamic acid  
CN erythro-L-4-Methylglutamic acid  
CN L-erythro-.gamma.-Methylglutamate  
CN L-erythro-.gamma.-Methylglutamic acid  
CN **SYM 2081**  
FS STEREOSEARCH  
MF C6 H11 N O4  
CI COM  
LC STN Files: ADISINSIGHT, BEILSTEIN\*, BIOSIS, CA, CAPLUS, CASREACT,  
CHEMCATS, CIN, CSCHEM, DRUGNL, DRUGUPDATES, PHAR, PROMT, TOXCENTER,  
USPATFULL  
(\*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



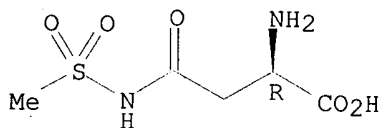
\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

72 REFERENCES IN FILE CA (1957 TO DATE)  
72 REFERENCES IN FILE CAPLUS (1957 TO DATE)

C=C[C@H](C(=O)O)[C@@H](R)[C@H](C(=O)O)N

3 REFERENCES IN FILE CA (1957 TO DATE)  
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

Absolute stereochemistry.



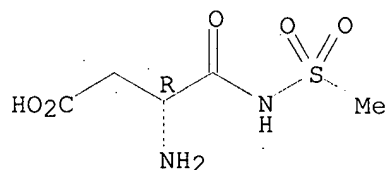
2 REFERENCES IN FILE CA (1957 TO DATE)  
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

Searched by Barb O'Bryen, STIC 308-4291

## OTHER NAMES:

CN **SYM 2051**  
FS STEREOSEARCH  
MF C5 H10 N2 O5 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2 REFERENCES IN FILE CA (1957 TO DATE)  
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> fil capl toxcenter uspatf; d que 117  
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L11 1 SEA FILE=REGISTRY ABB=ON "SYM 2083"/CN  
L12 1 SEA FILE=REGISTRY ABB=ON "SYM 2062"/CN  
L13 1 SEA FILE=REGISTRY ABB=ON "SYM 2051"/CN  
L14 6 SEA L11  
L15 5 SEA L12  
L16 5 SEA L13  
L17 6 SEA L14 OR L15 OR L16

*Registry #  
Search*

=> dup rem 117  
PROCESSING COMPLETED FOR L17  
L18 5 DUP REM L17 (1 DUPLICATE REMOVED)  
ANSWERS '1-3' FROM FILE CAPLUS  
ANSWERS '4-5' FROM FILE USPATFULL

=> d ibib ab hitrn 1-5

L18 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1  
ACCESSION NUMBER: 2002:391517 CAPLUS  
DOCUMENT NUMBER: 136:395975  
TITLE: Glutamate receptor ligands for modulation,  
stimulation, and inhibition of glutamate transport  
INVENTOR(S): Maccacchini, Maria-Luisa; Pei, Xue-Feng  
PATENT ASSIGNEE(S): Annovis, Inc., USA  
SOURCE: PCT Int. Appl., 48 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002040002	A2	20020523	WO 2001-US48448	20011030
W:				
AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:				
GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002037717	A5	20020527	AU 2002-37717	20011030
US 2002188022	A1	20021212	US 2001-21177	20011030
PRIORITY APPLN. INFO.:			US 2000-244252P P	20001030
			WO 2001-US48448 W	20011030

OTHER SOURCE(S): MARPAT 136:395975

AB The invention discloses the use of glutamate receptor ligands (agonists

and antagonists) for inhibiting, stimulating, modulating, or regulating glutamate reuptake. It has been discovered that such compds. can bind to or modulate glutamate transporters and affect extracellular glutamate levels by affecting transporter activity. The disclosed compds. can have a variety of effects on glutamate transporter activity including activation or inhibition. Such compds. are useful to treat various neurol. diseases and conditions involving glutamate transporter and glutamate receptor activation. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporters can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concn. Prodrug forms of transporter compds. can be used as drugs.

IT 284024-46-0, SYM 2083 284024-46-0D, derivs.

402578-41-0, SYM 2051 402578-67-0, SYM 2062

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

(glutamate receptor ligands for modulation, stimulation, and inhibition of glutamate transport)

L18 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:172225 CAPLUS

DOCUMENT NUMBER: 136:210595

TITLE: Screen for glutamate reuptake inhibitors, stimulators, and modulators

INVENTOR(S): Beart, Philip M.; O'Shea, Ross D.; Aprico, Karina;

Lawrence, Andrew J.; Maccicchini, Maria-luisa

PATENT ASSIGNEE(S): Annovis, Inc., USA; Monash University

SOURCE: PCT Int. Appl., 47 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018941	A2	20020307	WO 2001-US27323	20010831
WO 2002018941	A3	20020926		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001088658	A5	20020313	AU 2001-88658	20010831
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EP 1314041	A2	20030528	EP 2001-968408	20010831
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US 2002115688	A1	20020822	US 2001-944954	20010901
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PRIORITY APPLN. INFO.: US 2000-229952P P 20000901

US 2000-230159P P 20000901

WO 2001-US27323 W 20010831

OTHER SOURCE(S): MARPAT 136:210595

AB Disclosed is a method for identifying compds. that bind to or modulate a glutamate transporter. The disclosed method is useful for identifying compds. that can inhibit, stimulate, or modulate the activity of the glutamate transporter and thus affect glutamate reuptake. The method is a screening technique where compds. known to bind to glutamate receptors (for example, glutamate receptor ligands, including many agonists, and

SYM 2081

antagonists) are bound to a glutamate transporter and compds. are screened to identify those that can alter the binding of the glutamate receptor-binding compds. Compds. shown to alter the binding of the receptor-binding compds. Compds. shown to alter the binding of the receptor compds. from glutamate transporter in the disclosed assay can have a variety of effects on glutamate transporter in the disclosed assay can have a variety of effects on glutamate transporter activity including activation or inhibition. These compds. are expected to affect or interfere with glutamate reuptake by the glutamate transporter and thus can be used to modulate, stimulate, or inhibit glutamate reuptake. Such compds. are useful to treat various neurol. diseases and conditions involving glutamate transporter and glutamate receptor activation. One of the compds. is (2S,4R)-4-methylglutamate or [3H]-(2S,4R)-4-methylglutamate. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporter can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concn. Prodrug forms of transporter compds. are preferred for use as drugs.

IT 284024-46-0 402578-41-0 402578-67-0

RL: PAC (Pharmacological activity); BIOL (Biological study)  
(screening for glutamate reuptake inhibitors, stimulators, and modulators)

L18 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:321625 CAPLUS

DOCUMENT NUMBER: 133:99059

TITLE: 4-alkyl- and 4-cinnamylglutamic acid analogues are potent GluR5 kainate receptor agonists

AUTHOR(S): Pedregal, Concepcion; Collado, Ivan; Escríbano, Ana; Ezquerra, Jesus; Dominguez, Carmen; Mateo, Ana I.; Rubio, Almudena; Baker, S. Richard; Goldsworthy, John; Kamboj, Rajender K.; Ballyk, Barbara A.; Hoo, Ken; Bleakman, David

CORPORATE SOURCE: Lilly S.A., Madrid, 28108, Spain

SOURCE: Journal of Medicinal Chemistry (2000), 43(10), 1958-1968

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

SYM 2083

AB Enantiomerically pure (2S,4R)-4-substituted glutamic acids were prep'd. and tested for homomeric GluR5 and GluR6 kainate subtype receptor affinity. Some of the 4-cinnamyl analogs showed high selectivity and potency ( $K_i < 25$  nM) for the GluR5 receptors. The greatest selectivity and potency were achieved with the 3-(2-naphthyl)prop-2-enyl comp'd. This comp'd., LY339434, has negligible activity at the AMPA and kainate receptors GluR1, -2, -4 and -6. Although, LY339434 shows agonist activity at NMDA receptors in cultural hippocampal neurons (approx.  $EC_{50}$  of 2.5  $\mu$ M), we consider that LY339434 should be a useful pharmacol. tool for the investigation of the functional role of GluR5 kainate receptors.

IT 284024-46-0P, LY 310214

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(alkyl- and cinnamylglutamic acid analogs are potent GluR5 kainate receptor agonists)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 5 USPATFULL

ACCESSION NUMBER: 2002:330336 USPATFULL

TITLE: Methods for modulation, stimulation, and inhibition of glutamate reuptake



INVENTOR(S): Maccicchini, Maria-Luisa, West Chester, PA, UNITED STATES  
Pei, Xue-Feng, Lansdale, PA, UNITED STATES  
PATENT ASSIGNEE(S): Annovis. Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002188022	A1	20021212
APPLICATION INFO.:	US 2001-21177	A1	20011030 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-244252P	20001030 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400	

NUMBER OF CLAIMS: 9  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 13 Drawing Page(s)  
LINE COUNT: 1053

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method for inhibiting, stimulating, modulating, or regulating glutamate reuptake. The method makes use of compounds that are ligands of glutamate receptors, including many agonists, or antagonists of glutamate receptors. It has been discovered that such compounds can bind to or modulate glutamate transporters and affect extracellular glutamate levels by affecting transporter activity. The disclosed compounds can have a variety of effects on glutamate transporter activity including activation or inhibition. Such compounds are useful to treat various neurological diseases and conditions involving glutamate transporter and glutamate receptor activation. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporters can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concentration. Prodrug forms of transporter compounds can be used as drugs.

IT 284024-46-0, SYM 2083 284024-46-0D, derivs.  
402578-41-0, SYM 2051 402578-67-0, SYM 2062  
(glutamate receptor ligands for modulation, stimulation, and inhibition of glutamate transport)

L18 ANSWER 5 OF 5 USPATFULL

ACCESSION NUMBER: 2002:214299 USPATFULL  
TITLE: Screen for glutamate reuptake inhibitors, stimulators, and modulators

INVENTOR(S): Beart, Philip M., Ivanhoe, AUSTRALIA  
O'Shea, Ross D., Blackburn South, AUSTRALIA  
Aprico, Karina, Forest Hill, AUSTRALIA  
Lawrence, Andrew J., Brighton, AUSTRALIA  
Maccicchini, Maria-Luisa, West Chester, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002115688	A1	20020822
APPLICATION INFO.:	US 2001-944954	A1	20010901 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-229952P	20000901 (60)
	US 2000-230159P	20000901 (60)

DOCUMENT TYPE: Utility  
FILE SEGMENT: APPLICATION  
LEGAL REPRESENTATIVE: PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400

NUMBER OF CLAIMS: 27  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 14 Drawing Page(s)  
LINE COUNT: 1184

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method for identifying compounds that bind to or modulate a glutamate transporter. The disclosed method is useful for identifying compounds that can inhibit, stimulate, or modulate the activity of the glutamate transporter and thus affect glutamate reuptake. The method is a screening technique where compounds known to bind to glutamate receptors (for example, glutamate receptor ligands, including many agonists, and antagonists) are bound to a glutamate transporter and compounds are screened to identify those that can alter the binding of the glutamate receptor-binding compounds. Compounds shown to alter the binding of the receptor compounds from glutamate transporters in the disclosed assay can have a variety of effects on glutamate transporter activity including activation or inhibition. These compounds are expected to affect or interfere with glutamate reuptake by the glutamate transporter and thus can be used to modulate, stimulate, or inhibit glutamate reuptake. Such compounds are useful to treat various neurological diseases and conditions involving glutamate transporter and glutamate receptor activation. One of the compounds is (2S,4R)-4-methylglutamate or [<sup>sup</sup>.3H]-(2S,4R)-4-methylglutamate. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporters can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concentration. Prodrug forms of transporter compounds are preferred for use as drugs.

IT 284024-46-0 402578-41-0 402578-67-0  
(screening for glutamate reuptake inhibitors, stimulators, and modulators)

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FILE COVERS 1907 - 25 Jun 2003 VOL 138 ISS 26  
FILE LAST UPDATED: 24 Jun 2003 (20030624/ED)

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L5 11863 SEA FILE=CAPLUS ABB=ON GLUTAMATE RECEPTORS/CT  
L8 256906 SEA FILE=CAPLUS ABB=ON ?UPTAKE?  
L10 1 SEA FILE=REGISTRY ABB=ON "SYM 2081"/CN  
L19 72 SEA FILE=CAPLUS ABB=ON L10  
L20 1 SEA FILE=REGISTRY ABB=ON GLUTAMATE/CN  
L21 86003 SEA FILE=CAPLUS ABB=ON L20 OR GLUTAMATE#  
L22 48 SEA FILE=CAPLUS ABB=ON (L5 OR L21) AND L19  
L24 5 SEA FILE=CAPLUS ABB=ON L8 AND L22

L5 11863 SEA FILE=CAPLUS ABB=ON GLUTAMATE RECEPTORS/CT  
L10 1 SEA FILE=REGISTRY ABB=ON "SYM 2081"/CN  
L19 72 SEA FILE=CAPLUS ABB=ON L10  
L20 1 SEA FILE=REGISTRY ABB=ON GLUTAMATE/CN  
L21 86003 SEA FILE=CAPLUS ABB=ON L20 OR GLUTAMATE#  
L25 96279 SEA FILE=CAPLUS ABB=ON NERVOUS SYSTEM/CW  
L26 340576 SEA FILE=CAPLUS ABB=ON BRAIN/CW  
L27 142126 SEA FILE=CAPLUS ABB=ON NERVE/CW  
L28 78131 SEA FILE=CAPLUS ABB=ON (L25 OR L26 OR L27) (L) (DISEASE# OR  
DISORDER#)  
L29 7 SEA FILE=CAPLUS ABB=ON L28 AND L19 AND (L5 OR L21)

L83 11 L24 OR L29

=> fil biosis; d que 132; fil toxcenter; d que 140; fil uspatf; d que 149; dup rem  
183,132,140,149  
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FILE COVERS 1969 TO DATE.  
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT  
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 19 June 2003 (20030619/ED)

L10 1 SEA FILE=REGISTRY ABB=ON "SYM 2081"/CN  
L30 17 SEA FILE=BIOSIS ABB=ON L10  
L31 72397 SEA FILE=BIOSIS ABB=ON GLUTAMATE#  
L32 9 SEA FILE=BIOSIS ABB=ON L30 AND L31

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TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2003 vocabulary. See <http://www.nlm.nih.gov/mesh/summ2003.html> for a description on changes.

L10 1 SEA FILE=REGISTRY ABB=ON "SYM 2081"/CN  
L38 10 SEA FILE=TOXCENTER ABB=ON L10  
L39 39154 SEA FILE=TOXCENTER ABB=ON GLUTAMATE#  
L40 7 SEA FILE=TOXCENTER ABB=ON L38 AND L39

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 24 Jun 2003 (20030624/PD)  
FILE LAST UPDATED: 24 Jun 2003 (20030624/ED)  
HIGHEST GRANTED PATENT NUMBER: US6584613  
HIGHEST APPLICATION PUBLICATION NUMBER: US2003115652  
CA INDEXING IS CURRENT THROUGH 24 Jun 2003 (20030624/UPCA)  
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 24 Jun 2003 (20030624/PD)  
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2003  
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2003

>>> USPAT2 is now available. USPATFULL contains full text of the <<<  
>>> original, i.e., the earliest published granted patents or <<<  
>>> applications. USPAT2 contains full text of the latest US <<<  
>>> publications, starting in 2001, for the inventions covered in <<<  
>>> USPATFULL. A USPATFULL record contains not only the original <<<  
>>> published document but also a list of any subsequent <<<  
>>> publications. The publication number, patent kind code, and <<<  
>>> publication date for all the US publications for an invention <<<  
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<  
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>>> classifications, or claims, that may potentially change from <<<

&gt;&gt;&gt; the earliest to the latest publication.

&lt;&lt;&lt;

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L10 1 SEA FILE=REGISTRY ABB=ON "SYM 2081"/CN  
L49 3 SEA FILE=USPATFULL ABB=ON L10

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PROCESSING COMPLETED FOR L49

L84 26 DUP REM L83 L32 L40 L49 (4 DUPLICATES REMOVED)  
ANSWERS '1-11' FROM FILE CAPLUS  
ANSWERS '12-20' FROM FILE BIOSIS  
ANSWERS '21-23' FROM FILE TOXCENTER  
ANSWERS '24-26' FROM FILE USPATFULL

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L84 ANSWER 1 OF 26 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1  
ACCESSION NUMBER: 2002:391517 CAPLUS  
DOCUMENT NUMBER: 136:395975  
TITLE: **Glutamate** receptor ligands for modulation,  
stimulation, and inhibition of **glutamate**  
transport  
INVENTOR(S): Macccecchini, Maria-Luisa; Pei, Xue-Feng  
PATENT ASSIGNEE(S): Annovis, Inc., USA  
SOURCE: PCT Int. Appl., 48 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002040002	A2	20020523	WO 2001-US48448	20011030
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

AU 2002037717 A5 20020527 AU 2002-37717 20011030  
US 2002188022 A1 20021212 US 2001-21177 20011030  
PRIORITY APPLN. INFO.: US 2000-244252P P 20001030  
WO 2001-US48448 W 20011030

OTHER SOURCE(S): MARPAT 136:395975

AB The invention discloses the use of **glutamate** receptor ligands (agonists and antagonists) for inhibiting, stimulating, modulating, or regulating **glutamate reuptake**. It has been discovered that such compds. can bind to or modulate **glutamate** transporters and affect extracellular **glutamate** levels by affecting transporter activity. The disclosed compds. can have a variety of effects on **glutamate** transporter activity including activation or inhibition. Such compds. are useful to treat various neurol. diseases and conditions involving **glutamate** transporter and **glutamate** receptor activation. For example, excess extracellular **glutamate** is a cause of excessive activation of **glutamate** receptors. Stimulating **glutamate reuptake** by **glutamate** transporters can ameliorate excessive activation of **glutamate** receptors by reducing the extracellular **glutamate** concn. Prodrug forms of transporter compds. can be used as drugs.

IT 31137-74-3, SYM 2081

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**glutamate** receptor ligands for modulation, stimulation, and inhibition of **glutamate** transport)

L84 ANSWER 2 OF 26 CAPLUS COPYRIGHT 2003 ACS

DUPLICATE 2

ACCESSION NUMBER: 2000:182659 CAPLUS

DOCUMENT NUMBER: 132:289094

TITLE: Low-affinity kainate receptor agonists induce insult-dependent apoptosis and necrosis in cultured murine cortical neurons

AUTHOR(S): Moldrich, Randal X.; Beart, Philip M.; Pascoe, Catherine J.; Cheung, Nam S.

CORPORATE SOURCE: Department of Pharmacology, Monash University, Clayton, 3168, Australia

SOURCE: Journal of Neuroscience Research (2000), 59(6), 788-796

CODEN: JNREDK; ISSN: 0360-4012

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Overstimulation of ionotropic **glutamate** receptors leads to excitotoxic neuronal death, which has been implicated in the neurodegeneration of neurol. diseases. The present study examd. the role of putative low-affinity kainate receptor subtype (GluR5-7) agonists in excitotoxicity in cultured murine cortical neurons. The concn.-dependent decrease in cell viability induced by the agonists kainate (1-1000 .mu.M) and (RS)-2-amino-3-(hydroxy-5-tert-butylisoxazol-4-yl) propanoic acid (ATPA; 1-1000 .mu.M) was only attenuated by 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 10 .mu.M) and 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466; 20 .mu.M). (S)-5-iodowillardiine (1-1000 .mu.M)-induced toxicity was attenuated by CNQX (20 .mu.M), GYKI 52466 (20 .mu.M) and MK-801 (10 .mu.M); however, (2S,4R)-4-methylglutamate (1-120 .mu.M)-induced toxicity was not attenuated by the antagonists. None of the agonists possessed selective actions at GluR5-7. Morphol. observations (phase-contrast and fluorescence microscopy) revealed that the agonists induced two distinct patterns of neuronal injury. After 24 h of treatment, low concns. of agonists (1-30 .mu.M) produced cellular shrinkage and nuclear granulation consistent with slow, apoptotic-like neuronal death. Pyknotic labeling with the DNA binding dye Sytox green confirmed these apoptotic characteristics, which significantly decreased with increasing concns. After 4 h, increasing concns. of agonists

(100-1000  $\mu$ M) induced cellular swelling, with subsequent extracellular debris; labeling with propidium iodide revealed isolated nuclei consistent with the increased involvement of rapid necrosis. Thus, all putative GluR5-7 agonists produced excitotoxicity across a necrotic-apoptotic continuum in murine cortical neuron cultures.

IT 31137-74-3

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(low-affinity kainate receptor agonists induce insult-dependent apoptosis and necrosis in cultured murine cortical neurons)

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 3 OF 26 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3

ACCESSION NUMBER: 1999:567887 CAPLUS

DOCUMENT NUMBER: 131:281448

TITLE: Excitotoxic injury profiles of low-affinity kainate receptor agonists in cortical neuronal cultures

AUTHOR(S): Moldrich, Randal X.; Cheung, Nam S.; Pascoe, Catherine J.; Beart, Philip M.

CORPORATE SOURCE: Department of Pharmacology, Monash University, Clayton, 3168, Australia

SOURCE: European Journal of Pharmacology (1999), 378(2), R1-R3  
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Neurotoxic profiles of putative agonists for low-affinity kainate subtypes of L-glutamate receptors (GluR5-7) were detd. in cultured cortical neurons. Rank order of neurotoxic potency ( $\mu$ M): (S)-5-iodowillardiine (9)  $\approx$  (2S,4R,6E)-2-amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid (LY339434, 11) > (2S,4R)-4-methylglutamate (33) > kainate (100) > (RS)-2-amino-3-(hydroxy-5-tert-butylisoxazol-4-yl)propanoic acid (ATPA, 360). Using ionotropic glutamate receptor antagonists, neurotoxicity induced by kainate, ATPA and (S)-5-iodowillardiine appeared to involve a GluR5-7 component, unlike LY339434 and (2S,4R)-4-methylglutamate. These putative GluR5-7 agonists exhibited complex excitotoxic profiles highlighting the importance of studying native glutamate receptors.

IT 31137-74-3, (2S,4R)-4-Methylglutamic acid

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (excitotoxic injury profiles of low-affinity kainate receptor agonists in cortical neuronal cultures)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 4 OF 26 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 4

ACCESSION NUMBER: 1993:140037 CAPLUS

DOCUMENT NUMBER: 118:140037

TITLE: Glutamate uptake system in the presynaptic vesicle: Glutamic acid analogs as inhibitors and alternate substrates

AUTHOR(S): Winter, Harry C.; Ueda, Tetsufumi

CORPORATE SOURCE: Med. Sch., Univ. Michigan, Ann Arbor, MI, 48109, USA

SOURCE: Neurochemical Research (1993), 18(1), 79-85

CODEN: NEREDZ; ISSN: 0364-3190

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A variety of naturally occurring amino acids, their isomers, and synthetic analogs were tested for their ability to inhibit uptake of [3H] glutamate into presynaptic vesicles from bovine cerebral cortex. Strongest inhibition ( $K_i$  < 1 mM) was obsd. for trans-1-aminocyclopentane-

1,3-dicarboxylic acid (t-ACPD) and erythro-4-methyl-L-glutamic acid (MGlu), while 4-methylene-L-glutamic acid (MeGlu) was only moderately inhibitory ( $K_i = .\text{apprx.}3 \text{ mM}$ ), indicating that the synaptic vesicle **glutamate** translocator has higher affinity for trans-ACPD and MGlu than for **glutamate**. A few other amino acids, e.g., 4-hydroxyglutamic acid, S-carboxyethyl cysteine, and 5-fluorotryptophan, were slightly inhibitory; all L- and DL-isomers of protein amino acids and longer chain acidic amino acids were without measurable inhibition. Potassium tetrathionate and S-sulfocysteine exhibited strong to moderate noncompetitive or irreversible inhibition. Inhibition by t-ACPD, MGlu, or MeGlu was competitive with glutamic acid. Each of these competitive inhibitors was also taken up by the vesicle prepn. in an ATP-dependent manner, as indicated by their being recovered unchanged from filtered vesicles. Similar results were obtained with reconstituted vesicles, while **glutamate uptake** by partially purified rat synaptosomes was inhibited only by MGlu. These results indicate that the **glutamate** translocator of presynaptic vesicles has stringent structural requirements distinct from those of the plasma membrane translocator and the metabotropic type of postsynaptic **glutamate** receptor. They further suggest possible structural requirements of pharmacol. significant compds. that can substitute for glutamic acid in the presynaptic side of glutamatergic synapses, thus serving to moderate or control **glutamate** excitation and assocd. excitotoxic effects in these neurons.

IT 31137-74-3

RL: BIOL (Biological study)

(as **glutamate uptake** system inhibitors and alternate substrates, in cerebral cortex presynaptic vesicles, structure in relation to)

L84 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:172225 CAPLUS

DOCUMENT NUMBER: 136:210595

TITLE: Screen for **glutamate reuptake** inhibitors, stimulators, and modulators

INVENTOR(S): Beart, Philip M.; O'Shea, Ross D.; Aprico, Karina; Lawrence, Andrew J.; Maccecchini, Maria-luisa

PATENT ASSIGNEE(S): Annovis, Inc., USA; Monash University

SOURCE: PCT Int. Appl., 47 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018941	A2	20020307	WO 2001-US27323	20010831
WO 2002018941	A3	20020926		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2001088658	A5	20020313	AU 2001-88658	20010831
EP 1314041	A2	20030528	EP 2001-968408	20010831
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
US 2002115688	A1	20020822	US 2001-944954	20010901



## PRIORITY APPLN. INFO.:

US 2000-229952P P 20000901  
US 2000-230159P P 20000901  
WO 2001-US27323 W 20010831

OTHER SOURCE(S): MARPAT 136:210595

AB Disclosed is a method for identifying compds. that bind to or modulate a **glutamate** transporter. The disclosed method is useful for identifying compds. that can inhibit, stimulate, or modulate the activity of the **glutamate** transporter and thus affect **glutamate reuptake**. The method is a screening technique where compds. known to bind to **glutamate** receptors (for example, **glutamate** receptor ligands, including many agonists, and antagonists) are bound to a **glutamate** transporter and compds. are screened to identify those that can alter the binding of the **glutamate** receptor-binding compds. Compds. shown to alter the binding of the receptor-binding compds. shown to alter the binding of the receptor compds. from **glutamate** transporter in the disclosed assay can have a variety of effects on **glutamate** transporter in the disclosed assay can have a variety of effects on **glutamate** transporter activity including activation or inhibition. These compds. are expected to affect or interfere with **glutamate reuptake** by the **glutamate** transporter and thus can be used to modulate, stimulate, or inhibit **glutamate reuptake**. Such compds. are useful to treat various neurol. diseases and conditions involving **glutamate** transporter and **glutamate** receptor activation. One of the compds. is (2S,4R)-4-methylglutamate or [3H]-(2S,4R)-4-methylglutamate. For example, excess extracellular **glutamate** is a cause of excessive activation of **glutamate** receptors. Stimulating **glutamate reuptake** by **glutamate** transporter can ameliorate excessive activation of **glutamate** receptors by reducing the extracellular **glutamate** concn. Prodrug forms of transporter compds. are preferred for use as drugs.

IT 31137-74-3

RL: PAC (Pharmacological activity); BIOL (Biological study)  
(screening for **glutamate reuptake** inhibitors,  
stimulators, and modulators)

L84 ANSWER 6 OF 26 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:651760 CAPLUS

DOCUMENT NUMBER: 136:95915

TITLE: Excitotoxic profiles of novel, low-affinity kainate  
receptor agonists in primary cultures of murine  
cerebellar granule cells

AUTHOR(S): Giardina, S. F.; Beart, P. M.

CORPORATE SOURCE: Department of Pharmacology, Monash University,  
Clayton, 3800, AustraliaSOURCE: Neuropharmacology (2001), 41(4), 421-432  
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The involvement of low-affinity kainate (KA) receptors in neuronal injury was investigated by employing a variety of agonists active at GluR5-7. Their excitotoxic profiles were detd. in primary cultures of cerebellar granule cells, which abundantly expressed low-affinity KA receptors, and in the absence of any AMPA receptor-mediated neurotoxicity. Neurotoxicity induced by these compds. was analyzed by phase contrast microscopy, a cell viability assay, the TUNEL technique (apoptosis), and by employing propidium iodide (PI; necrosis). All agonists induced concn.-dependent neurotoxicity, with rank order (EC50 values; .mu.M): (S)-iodowillardiine (IW) 0.2 > (2S,4R)-4-methylglutamate (4-MG) 36 > (2S,4R,6E)-2-amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid (LY339434) 46 > KA 74 > (RS)-2-amino-3-(3-hydroxy-5-tert-butylisoxazol-4-yl)propanoic acid (ATPA) 88. IW exposure resulted in apoptosis at lower concns. (<30 .mu.M) and necrosis at higher

concns., both of which were attenuated by CNQX (50 .mu.M), but not MK-801 (10 .mu.M). ATPA-mediated neurotoxicity was purely apoptotic and was attenuated by the non-NMDA receptor antagonists. Both IW and ATPA induced injury with the morphol. characteristics of apoptosis shown by the presence of TUNEL-pos. neurons. LY339434-mediated neuronal injury was only attenuated by MK-801 and was necrotic in nature. Similarly, 4-MG (>30 .mu.M) exposure caused necrosis that was partially attenuated by MK-801 (10 .mu.M) and CNQX (50 .mu.M). The patterns of neurotoxicity possessed a complex pharmacol. profile, demonstrated an apoptotic-necrotic continuum and were inconsistent with past findings, further outlining the importance of characterizing novel compds. at native receptors. ATPA and to a lesser extent IW appear to be suitable drugs for low-affinity KA receptors. Since toxicity-mediated by low-affinity KA receptors seem likely to contribute to neurodegenerative conditions, our study importantly examines the excitotoxic profile of these novel agonists.

IT 31137-74-3

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(excitotoxic profiles of novel, low-affinity kainate receptor agonists  
in primary cultures of murine cerebellar granule cells)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:142167 CAPLUS

DOCUMENT NUMBER: 132:306711

TITLE: SYM-2081 a kainate receptor antagonist reduces  
allodynia and hyperalgesia in a freeze injury model of  
neuropathic pain

AUTHOR(S): Ta, L. E.; Dionne, R. A.; Friction, J. R.; Hodges, J.  
S.; Kajander, K. C.

CORPORATE SOURCE: Department of Diagnostic and Surgical Sciences,  
University of Minnesota, Minneapolis, MN, USA

SOURCE: Brain Research (2000), 858(1), 106-120  
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cold-freeze injury at -4.degree.C to the rat sciatic nerve produces mech.  
allodynia and thermal hyperalgesia. The NMDA receptor, an excitatory  
amino acid (EAA) receptor, appears to be involved in the development of  
allodynia and hyperalgesia following nerve injury. The role, if any, of  
the kainate receptor, another EAA receptor, remains unknown. In the  
current study, the authors evaluated whether (2S,4R)-4-methylglutamic acid  
(SYM-2081), a recently developed kainate receptor antagonist, attenuates  
increased responsiveness following cold injury to the sciatic nerve.  
During baseline testing, Sprague-Dawley rats were evaluated for frequency  
of withdrawal from von Frey filaments and latency of withdrawal from a  
radiant thermal source. Animals were then anesthetized, the left sciatic  
nerve was exposed, and the nerve was cooled to -4.degree.C for 15 min  
(n=24). For control rats (n=24), all procedures were identical except  
that the nerve was maintained at 37.degree.C. Testing resumed on the  
third day following surgery. On the fifth post-operative day, SYM-2081  
(150 or 100 mg/kg), fentanyl citrate (0.04 mg/kg) or vehicle was injected  
i.p. Injury to the rat sciatic nerve induced a significant increase in  
withdrawal frequency and a significant decrease in withdrawal latency  
(ANOVA, p<0.05). SYM-2081 and fentanyl significantly reduced these  
responses (p<0.05). These results suggest that kainate and opioid  
receptors are involved in the mech. allodynia and thermal hyperalgesia  
that develop following cold injury to the sciatic nerve.

IT 31137-74-3, SYM-2081

RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES  
(Uses)

(kainate receptor and opioid receptor involvement in allodynia and hyperalgesia in freeze injury model of neuropathic pain and therapeutic potential of receptor antagonists)

REFERENCE COUNT: 114 THERE ARE 114 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 8 OF 26 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:256215 CAPLUS

DOCUMENT NUMBER: 131:53927

TITLE: The kainate receptor antagonist 2S,4R-4-methylglutamate attenuates mechanical allodynia and thermal hyperalgesia in a rat model of nerve injury  
AUTHOR(S): Sutton, J. L.; Maccacchini, M.-L.; Kajander, K. C.  
CORPORATE SOURCE: Department of Oral Science, and Graduate Program in Neuroscience, University of Minnesota, Minneapolis, MN, 55455, USA

SOURCE: Neuroscience (Oxford) (1999), 91(1), 283-292  
CODEN: NRSCDN; ISSN: 0306-4522

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Opioids and receptor antagonists of excitatory amino acids attenuate mech. allodynia and thermal hyperalgesia in animal models of neuropathic pain. Recently, a kainate receptor antagonist, 2S,4R-4-methylglutamate, has been developed but has not been tested for antinociceptive effects in animal models of neuropathic pain. We evaluated whether 2S,4R-4-methylglutamate attenuated responses to mech. and thermal stimuli in uninjured (control) rats and increased responsiveness in rats with chronic constriction injury. Rats were tested for a no. of withdrawal responses using a calibrated von Frey filament (mech. stimulus) and withdrawal latencies from a radiant heat source (thermal stimulus). In control rats, 2S,4R-4-methylglutamate produced a small but significant decrease in responses from the mech. stimulus (25 mg/kg) and significantly increased withdrawal latencies from the thermal stimulus at the highest dose administered (100 mg/kg). In addn., 2S,4R-4-methylglutamate greatly attenuated increased responsiveness in rats with chronic constriction injury. At four to eight days following chronic constriction injury, animals that displayed increased responsiveness to mech. and thermal stimuli were injected i.p. with either dizocilpine maleate (0.1 mg/kg), morphine (4 mg/kg), vehicle as controls, or 2S,4R-4-methylglutamate (25, 50, 75 or 100 mg/kg). 2S,4R-4-Methylglutamate (25, 50, 75 and 100 mg/kg) significantly attenuated the frequency of responses to mech. stimuli (Wilcoxon,  $P < 0.05$ ) and the latency of responses to thermal stimuli (anal. of variance and Duncan's,  $P < 0.05$ ). Dizocilpine maleate and morphine, as expected, also reduced these responses. These results suggest that, in addn. to opioid and N-methyl-D-aspartate receptors, kainate receptors may play a role in the maintenance of mech. allodynia and thermal hyperalgesia assocd. with peripheral nerve injury.

IT 31137-74-3

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(2S,4R-4-methylglutamate attenuation of and receptor mediation of mech. allodynia and thermal hyperalgesia in nerve injury)

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 9 OF 26 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:339244 CAPLUS

DOCUMENT NUMBER: 133:221159

TITLE: Low-affinity kainate receptor subunit-specific agonist, (2S,4R)-4-methylglutamate (SYM-2081), does

not induce neuronal cell death in rat hippocampal formation

AUTHOR(S): Okazaki, Mitsuhiro; Kitamura, Yoshihisa; Matsuoka, Yasuji

CORPORATE SOURCE: Department of Neurobiology, Kyoto Pharmaceutical University, Kyoto, 607-8412, Japan

SOURCE: Journal of Brain Science (1999), 25(1 & 2), 3-10  
CODEN: JBSCF5; ISSN: 1341-5301

PUBLISHER: PJD Publications Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Kainic acid (KA) induces neuronal cell death and glial activation in the hippocampal CA3 subfield of rat brain. This neuronal and glial activation is partly mediated by activation of the kainate receptor. The kainate receptors were divided into low- and high-affinity kainate receptor subunits, GluR5-7 and KA1/2, resp. In this study, we tried to clarify how low-affinity kainate receptor subunits participate in neurodegeneration using the specific agonist (2S, 4R)-4-methylglutamate (SYM-2081) by a comparison with KA. In this study, KA induced neuronal death, activation of microglia, and the transient loss of astrocytes. In contrast, the injection of SYM-2081 did not affect neurons or glia. Phosphorylation of c-Jun, an important step in neuronal apoptosis, was obsd. after the injection of KA. However, SYM-2081 did not phosphorylate c-Jun. These results suggest that the low-affinity kainate receptor subunits were less important for neuronal and glial activation, and that the high-affinity kainate receptor subunits may play more crit. roles in KA-induced neurodegeneration.

IT 31137-74-3, SYM-2081

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(low-affinity kainate receptor subunits role in neurodegeneration)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 10 OF 26 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:154392 CAPLUS

DOCUMENT NUMBER: 128:278857

TITLE: A novel kainate receptor ligand [3H]-(2S,4R)-4-methylglutamate: pharmacological characterization in rabbit brain membranes

AUTHOR(S): Toms, N. J.; Reid, M. E.; Phillips, W.; Kemp, M. C.; Roberts, P. J.

CORPORATE SOURCE: Department of Pharmacology, School of Medical Sciences, University of Bristol, Bristol, BS8 1TD, UK

SOURCE: Neuropharmacology (1998), Volume Date 1997, 36(11/12), 1483-1488  
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Since kainate evokes large non-desensitizing currents at .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, kainate is of limited use in discriminating between AMPA and kainate receptors. Following recent reports that (2S,4R)-4-methylglutamate is a kainate receptor-selective agonist, we have radiolabeled and subsequently characterized the binding of [3H]-(2S,4R)-4-methylglutamate to rabbit whole-brain membranes. [3H]-(2S,4R)-4-methylglutamate binding was rapid, reversible and labeled two sites (KD1 = 3.67 +/- 0.50 nM/Bmax1 = 0.54 +/- 0.03 pmol/mg protein and KD2 = 281.66 +/- 12.33 nM/Bmax2 = 1.77 +/- 0.09 pmol/mg protein). [3H]-(2S,4R)-4-methylglutamate binding was displaced by several non-NMDA receptor ligands: domoate > kainate .mchgt. L-quisqualate .gtoreq. L-glutamate > 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) .mchgt. (S)-AMPA = (S)-5-fluorowillardiine > NMDA. Neither the metabotropic

**glutamate** receptor agonists (1S,3R)-ACPD or L-AP4, together with the L-**glutamate uptake** inhibitor L-trans-2,4-PDC, influenced binding when tested at 100  $\mu$ M. We conclude that [3H]-(2S,4R)-4-methylglutamate is a useful radioligand for labeling kainate receptors. It possesses high selectivity, and possesses a pharmacol. similar to that for rat cloned low-affinity (Glu5 and 6) kainate receptor subunits.

IT 31137-74-3, (2S,4R)-4-Methylglutamic acid

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(pharmacol. in brain membranes of [3H]-(2S,4R)-4-methylglutamate as selective kainate receptor ligand)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 11 OF 26 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:129242 CAPLUS

DOCUMENT NUMBER: 128:252839

TITLE: DL-threo-.beta.-Benzyloxyaspartate, a potent blocker of excitatory amino acid transporters

AUTHOR(S): Shimamoto, Keiko; Lebrun, Bruno; Yasuda-Kamatani, Yoshimi; Sakaitani, Masahiro; Shigeri, Yasushi; Yumoto, Noboru; Nakajima, Terumi

CORPORATE SOURCE: Suntory Institute for Bioorganic Research, Osaka, 618, Japan

SOURCE: Molecular Pharmacology (1998), 53(2), 195-201

CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB DL-Threo-.beta.-Benzyloxyaspartate (DL-TBOA), a novel deriv. of DL-threo-.beta.-hydroxyaspartate, was synthesized and examd. as an inhibitor of sodium-dependent **glutamate**/aspartate (excitatory amino acid) transporters. DL-TBOA inhibited the **uptake** of [14C] **glutamate** in COS-1 cells expressing the human excitatory amino acid transporter-1 (EAAT1) ( $K_i = 42 \mu$ M) with almost the same potency as DL-threo-.beta.-hydroxyaspartate ( $K_i = 58 \mu$ M). With regard to the human excitatory amino acid transporter-2 (EAAT2), the inhibitory effect of DL-TBOA ( $K_i = 5.7 \mu$ M) was much more potent than that of dihydrokainate ( $K_i = 79 \mu$ M), which is well known as a selective blocker of this subtype. Electrophysiol., DL-TBOA induced no detectable inward currents in *Xenopus laevis* oocytes expressing human EAAT1 or EAAT2. However, it significantly reduced the **glutamate**-induced currents, indicating the prevention of transport. The dose-response curve of **glutamate** was shifted by adding DL-TBOA without a significant change in the max. current. The  $K_b$  values for human EAAT1 and EAAT2 expressed in *X. laevis* oocytes were 9.0  $\mu$ M and 116 nM, resp. These results demonstrated that DL-TBOA is, so far, the most potent competitive blocker of **glutamate** transporters. DL-TBOA did not show any significant effects on either the ionotropic or metabotropic **glutamate** receptors. Moreover, DL-TBOA is chem. much more stable than its benzoyl analog, a previously reported blocker of excitatory amino acid transporters; therefore, DL-TBOA should be a useful tool for investigating the physiol. roles of transporters.

IT 31137-74-3

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(DL-threo-.beta.-benzyloxyaspartate, a potent blocker of excitatory amino acid transporters)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L84 ANSWER 12 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2003:135828 BIOSIS  
DOCUMENT NUMBER: PREV200300135828  
TITLE: Low-affinity kainate receptor-mediated events reduce the protective activity of phenobarbital and diphenylhydantoin against maximal electroshock in mice.  
AUTHOR(S): Borowicz, K. K.; Zadzorniak, M.; Czuczwar, S. J. (1)  
CORPORATE SOURCE: (1) Department of Pathophysiology, Lublin Medical University, Jaczewskiego 8, Lublin, 20-090, Poland: czuczwar@galen.imw.lublin.pl Poland  
SOURCE: Neuropharmacology, (December 2002, 2002) Vol. 43, No. 7, pp. 1082-1086. print.  
ISSN: 0028-3908.

DOCUMENT TYPE: Article  
LANGUAGE: English

AB (2S,2R)-4-Methylglutamic acid (SYM 2081), a potent selective agonist of GluR5 and GluR6 kainate receptor subtypes, applied at the dose of 15.5 mg/kg, equal to its CD16 value (i.e., a dose required to induce convulsions in 16% of mice), significantly decreased the electroconvulsive threshold from 7.0 to 5.8 mA. When administered at the dose of 11.5 mg/kg, equal to 75% of its CD16, it markedly attenuated the protective activity of phenobarbital and diphenylhydantoin, but not that of valproate, carbamazepine, or diazepam against maximal electroshock-induced seizures in mice. The respective ED50 values were increased from 18.5 to 23.8 mg/kg for phenobarbital, and from 11.7 to 14.7 mg/kg for diphenylhydantoin. Since the free plasma levels of both antiepileptic drugs were not influenced by SYM 2081, the pharmacokinetic interaction does not seem to be involved in the observed results. In conclusion, low-affinity kainate receptor-mediated events might be a factor reducing the protective efficacy of some antiepileptic drugs. Furthermore, the activation of GluR5 and GluR6 kainate receptor subtypes by endogenous **glutamate** during seizures may be associated with the drug-resistance phenomenon.

L84 ANSWER 13 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2003:282284 BIOSIS  
DOCUMENT NUMBER: PREV200300282284  
TITLE: AMPA RATHER THAN KAINATE RECEPTORS MEDIATE ACETYLCHOLINE RELEASE FROM RABBIT RETINA.  
AUTHOR(S): Firth, S. I. (1); Massey, S. C.; Li, W.; Marshak, D. W. (1)  
CORPORATE SOURCE: (1) Neurobiol. and Anatomy, UT-Med School, Houston, TX, USA  
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 158.2.  
<http://sfn.scholarone.com.cd-rom>.  
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002  
Society for Neuroscience

DOCUMENT TYPE: Conference  
LANGUAGE: English

AB Cholinergic amacrine cells are a major type of local circuit neuron in the mammalian retina. Excitatory input to the cholinergic amacrine cells is via **glutamate** receptors of the AMPA/kainate type (Linn et al, 1991). The goal was to determine which receptor subtypes mediate this response. An in vivo, rabbit eyecup was preloaded with (3H)-choline, and the (3H)-ACh released into the superfusate was monitored (Massey & Redburn, 1982). A photopic, 3 Hz flash increased ACh release, and this light response was blocked by the specific AMPA receptor antagonists, GYKI 53655. Nonselective AMPA/kainate agonists also increased the release of ACh, but the specific kainate receptor agonist, SYM 2081 did not increase ACh release. We concluded that the excitatory input due to the light stimulus is mediated by AMPA receptors. We labeled lightly fixed retinas with antisera to either GluR 1, GluR 2/3 or GluR 4, the subunits found in AMPA receptors and ChAT. Many labeled punctae were observed in the inner

plexiform layer with each of the GluR antisera. However, there were no GluR 1-IR punctae on ChAT-IR dendrites. There were a few GluR 2/3-IR punctae, but more commonly, GluR 4-IR punctae were found on the ChAT-IR dendrites. The same was true of dye-injected cholinergic cells. Based on studies of recombinant AMPA receptor subunits, excitatory synapses where GluR 4 predominate are expected to be particularly strong (Swanson et al, 1997). Generally responses of AMPA receptors to **glutamate** rapidly desensitize and recover from desensitization, and this may account, at least in part, for the sensitivity of cholinergic cells to moving stimuli (O'Malley & Masland, 1993).

L84 ANSWER 14 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:509712 BIOSIS

DOCUMENT NUMBER: PREV200100509712

TITLE: Presynaptic kainate receptors at hippocampal mossy fiber synapses.

AUTHOR(S): Schmitz, Dietmar; Mellor, Jack; Frerking, Matthew; Nicoll, Roger A. (1)

CORPORATE SOURCE: (1) Departments of Cellular and Molecular Pharmacology and Physiology, University of California, San Francisco, CA, 94143: nicoll@phy.ucsf.edu USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (September 25, 2001) Vol. 98, No. 20, pp. 11003-11008. print.  
ISSN: 0027-8424.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Hippocampal mossy fibers, which are the axons of dentate granule cells, form powerful excitatory synapses onto the proximal dendrites of CA3 pyramidal cells. It has long been known that high-affinity binding sites for kainate, a **glutamate** receptor agonist, are present on mossy fibers. Here we summarize recent experiments on the role of these presynaptic kainate receptors (KARs). Application of kainate has a direct effect on the amplitude of the extracellularly recorded fiber volley, with an enhancement by low concentrations and a depression by high concentrations. These effects are mediated by KARs, because they persist in the presence of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-selective antagonist GYKI 53655, but are blocked by the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/KAR antagonist 6-cyano-7-nitroquinoxaline-2,3-dione and the KAR antagonist SYM2081. The effects on the fiber volley are most likely caused by a depolarization of the fibers via the known ionotropic actions of KARs, because application of potassium mimics the effects. In addition to these effects on fiber excitability, low concentrations of kainate enhance transmitter release, whereas high concentrations depress transmitter release. Importantly, the synaptic release of **glutamate** from mossy fibers also activates these presynaptic KARs, causing an enhancement of the fiber volley and a facilitation of release that lasts for many seconds. This positive feedback contributes to the dramatic frequency facilitation that is characteristic of mossy fiber synapses. It will be interesting to determine how widespread facilitatory presynaptic KARs are at other synapses in the central nervous system.

L84 ANSWER 15 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:562766 BIOSIS

DOCUMENT NUMBER: PREV200100562766

TITLE: Expression of functional **glutamate** transporter GLT-1 (EAAT2) in adult neurons.

AUTHOR(S): Suchak, S. K. (1); Baloyianni, N. (1); Meldrum, B. S. (1); Rattray, M. (1)

CORPORATE SOURCE: (1) Centre for Neuroscience Research, GKT Sch Biomed Sci, King's College London, London UK

SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 1873. print.  
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001  
ISSN: 0190-5295.

DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB The five members of the Excitatory Amino Acid Transporter family, EAAT1 (GLAST), EAAT2 (GLT-1), EAAT3 (EAAC1), EAAT4 and EAAT5, play vital roles in recycling **glutamate** and controlling synaptic **glutamate** levels. The "glial" transporter EAAT2 accounts for 90% of total CNS **glutamate** uptake. Evidence suggests that neurons are capable of high affinity, sodium-dependent **glutamate** uptake, but the identity of the EAATs involved are unknown. Cultured neurons express several EAAT isoforms including EAAT2. In vivo, EAAT2 mRNA, but not significant levels of protein, have been detected within subsets of neurons, including cerebral cortex and hippocampal neurons. Pharmacological and biochemical approaches were employed to determine which **glutamate** transporters are functional in adult neurons and glia. Rat and mouse synaptosomes and Glial Plasmalemmal Vesicles (GPV) were prepared and uptake of 3H-l-**glutamate** or 3H-d-aspartate measured to estimate neuronal and glial uptake. Radioligand uptake was higher in GPV than synaptosomes (240pmol/mg/min v 10pmol/min/mg). A variety of drugs were used to block uptake: DHK, SYM2081 and PDC, all showing greater specificity for EAAT2 over the other EAATs; T3MG which only shows activity at EAAT2; and SOS with a 10 fold greater affinity for EAAT1 than EAAT2. GPV and synaptosomes had similar pharmacological profiles, suggesting neurons predominantly expressed EAAT2. Western blotting determined expression of EAAT1 and EAAT2 in both synaptosomes and GPVs. EAAT2 levels in the synaptosomes were 11% of GPV levels. The study indicates that the main **glutamate** transporter in nerve terminals is EAAT2.

L84 ANSWER 16 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:534323 BIOSIS

DOCUMENT NUMBER: PREV200100534323

TITLE: Antinociceptive effects of GluR5 kainate receptor agonists in normal and sensitized states: A role for gabaergic mechanisms.

AUTHOR(S): Mascias, B. (1); Herrero, J. F.; Chizh, B. A. (1)

CORPORATE SOURCE: (1) Pharmacology, Grunenthal GmbH R and D, Aachen Germany

SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 1270. print.  
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001  
ISSN: 0190-5295.

DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB GluR5 receptors have been shown to modulate spinal nociception, however, their role in nociceptive hypersensitivity remains unclear. We have investigated the antinociception by GluR5 agonists in acute and hyperalgesic states. Moreover, as gabaergic mechanisms may be involved in the effects of GluR5 ligands in some brain structures, we queried if they play a role in spinal antinociception. The GluR5/6 agonist, SYM2081, and the GluR5 selective agonist, ATPA, were tested in vitro in spinal cord preparations from immature rats with or without peripheral carrageenan inflammation, and behaviourally on mechanical nociceptive thresholds. Both SYM2081 (100 mg/kg i.p.) and ATPA (5 mg/kg i.p.) were antihyperalgesic in behavioural tests. In vitro, ATPA (0.01-3  $\mu$ M), but not SYM2081 (0.1-10



muM), dose-dependently inhibited ventral root responses to high intensity single and repetitive (1 Hz) dorsal root stimulation and the rate of cumulative depolarisation. Low intensity evoked responses were only marginally inhibited by ATPA. There was no significant difference between inflamed and non-inflamed preparations in vitro. The antinociceptive effect of ATPA (1 muM) in vitro was substantially attenuated in the presence of the GABAA antagonist bicuculline (10 muM). We conclude that GluR5 kainate receptors modulate spinal nociceptive transmission in normal and sensitized states. The antinociceptive action of GluR5 agonists may involve gabaergic mechanisms in the spinal cord. The difference between the two GluR5 agonists in vitro could be explained by their different subtype selectivity or receptor desensitization profiles.

L84 ANSWER 17 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:298613 BIOSIS

DOCUMENT NUMBER: PREV200100298613

TITLE: **Glutamate** receptor subtypes in horizontal cells in the human retina.

AUTHOR(S): Shen, W. (1); Slaughter, M. M. (1)

CORPORATE SOURCE: (1) Depts of Physiol and Biophysics, and Ophthalmology, SUNY at Buffalo, Buffalo, NY USA

SOURCE: IOVS, (March 15, 2001) Vol. 42, No. 4, pp. S509. print. Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 29-May 04, 2001

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L84 ANSWER 18 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:87454 BIOSIS

DOCUMENT NUMBER: PREV200100087454

TITLE: Non-NMDA **glutamate** receptor mediated currents in AII amacrine cells in the rat retina.

AUTHOR(S): Morkve, S. H. (1); Hartveit, E.

CORPORATE SOURCE: (1) University of Bergen, Bergen Norway

SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-248 12. print. Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience . ISSN: 0190-5295.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

AB AII amacrine cells receive the majority of their bipolar input from rod bipolar cells, with **glutamate** being the likely transmitter candidate. They express ionotropic **glutamate** receptors of both the NMDA and the non-NMDA type. Non-NMDA receptors are classified as either AMPA or kainate receptors. The lack of specificity of the agonists AMPA and kainate for their respective receptors, however, impedes the discrimination between these receptors. The question therefore arises whether the non-NMDA receptors expressed by AII amacrine cells are of the AMPA or kainate type, or both. In order to address this, we have obtained whole-cell voltage-clamp recordings (Cs-glucuronate, TEA, +/- spermine) from visually identified AII amacrine cells in vertical slices of rat retina. Drugs were applied in the bath and by pressure from a multi-barrel pipette complex. Both AMPA and kainate evoked a conductance increase with current reversal close to 0 mV and the currents were blocked by CNQX. The current-voltage relationship of both AMPA and kainate displayed no rectification, independent of the presence of spermine intracellularly. From concentration-response curves for AMPA, EC50 and the Hill coefficient were calculated as approx 50 muM and 1.2. The corresponding values for

kainate were apprx 75  $\mu$ M and 2.0. The response to AMPA was potentiated by the drug cyclothiazide, presumably by blocking receptor desensitization. The non-competitive AMPA receptor antagonist GYKI 53655 blocked the response to both AMPA and kainate. Because kainate receptors exhibit a strongly desensitizing response to kainate, we have attempted to reveal a putative response by blocking this desensitization with concanavalin A. Treatment with conA has not revealed a response to kainate or the kainate receptor-specific agonist SYM 2081. We therefore conclude that AMPA receptors (with no  $\text{Ca}^{2+}$  permeability), but not kainate receptors, will be involved in mediating glutamatergic input to AII amacrine cells.

L84 ANSWER 19 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 2000:146909 BIOSIS  
DOCUMENT NUMBER: PREV200000146909  
TITLE: Effects of concanavalin A on functionally expressed GluR6 detected with aequorin in a stable cell line.  
AUTHOR(S): Kronbach, C. (1); Mueller, K. (1); Rosenkranz, I. (1); Kronbach, T. (1)  
CORPORATE SOURCE: (1) Dept. Biochemistry, Corporate R and D ASTA Medica AG, Arzneimittelwerk Dresden, Meissner Str. 191, 01445, Radebeul Germany  
SOURCE: Society for Neuroscience Abstracts., (1999) Vol. 25, No. 1-2, pp. 1489.  
Meeting Info.: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999  
Society for Neuroscience  
. ISSN: 0190-5295.  
DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L84 ANSWER 20 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 1997:113898 BIOSIS  
DOCUMENT NUMBER: PREV199799413101  
TITLE: (2S,4R)-4-methylglutamic acid (SYM 2081): A selective, high-affinity ligand for kainate receptors.  
AUTHOR(S): Zhou, L.-M.; Gu, Z.-Q.; Costa, A. M.; Yamada, K. A.; Mansson, P. E.; Giordano, T.; Skolnick, P.; Jones, K. A. (1)  
CORPORATE SOURCE: (1) Synaptic Pharm. Corp., 215 College Rd., Paramus, NJ 07652 USA  
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1997) Vol. 280, No. 1, pp. 422-427.  
ISSN: 0022-3565.  
DOCUMENT TYPE: Article  
LANGUAGE: English

AB Glutamic acid activates ionotropic **glutamate** receptors that mediate excitatory transmission in the central nervous system. The introduction of a methyl group at position 4 of glutamic acid imparts selectivity for kainate receptors, relative to other (N-methyl-D-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) ionotropic **glutamate** receptors. Among the stereoisomers of 4-methylglutamic acid, the potency of the (2S,4R)-isomer (SYM 2081) to inhibit (3H)kainic acid binding to both wild-type (rat forebrain) and recombinant (GluR6) kainate receptors (IC-50 values of apprx 32 and 19 nM, respectively) was comparable to that of kainic acid (IC-50 values of apprx 13 and 28 nM, respectively). SYM 2081 was apprx 800- and 200-fold less potent as an inhibitor of radioligand binding to wild-type (rat forebrain) alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartate receptors, respectively. Preexposure of human embryonic kidney 293 cells stably expressing GluR6 receptors to low concentrations of SYM 2081 (30-300 nM) resulted in a reversible blockade of the rapidly desensitizing currents produced by kainate application. At

higher concentrations, SYM 2081 (EC-50 of approx 1  $\mu$ -M) elicited kainate-like, rapidly desensitizing, inward currents. Pretreatment of recombinant GluR6 receptors with concanavalin A both abolished the effect of SYM 2081 to block kainate-induced currents and revealed nondesensitizing currents induced by SYM 2081 alone. The latter observations provide strong support for the hypothesis that SYM 2081 blocks kainate-induced currents through a process of agonist-induced desensitization. SYM 2081 also activated alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor currents in primary cultures of cerebral cortex and, consistent with data obtained by radioligand binding, was approx 5-fold less potent than kainate (EC-50 values of 325 and 70  $\mu$ -M, respectively) in this measure. SYM 2081 is a high-affinity, selective, kainate agonist that may prove useful both as a probe to examine the physiological functions of kainate receptors and as the prototype of a novel class of therapeutic agents.

L84 ANSWER 21 OF 26 TOXCENTER COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2002:79116 TOXCENTER  
COPYRIGHT: Copyright 2003 ACS  
DOCUMENT NUMBER: CA13707087834U  
TITLE: Evaluation of drugs acting at **glutamate** transporters in organotypic hippocampal cultures: new evidence on substrates and blockers in excitotoxicity  
AUTHOR(S): O'Shea, Ross D.; Fodera, Melissa V.; Aprico, Karina; Dehnes, Yvette; Danbolt, Niels C.; Crawford, Duncan; Beart, Philip M.  
CORPORATE SOURCE: Department of Pharmacology, Monash University, Vic, 3800, Australia.  
SOURCE: Neurochemical Research, (2002) Vol. 27, No. 1/2, pp. 5-13.  
CODEN: NEREDZ. ISSN: 0364-3190.  
COUNTRY: AUSTRALIA  
DOCUMENT TYPE: Journal  
FILE SEGMENT: CAPLUS  
OTHER SOURCE: CAPLUS 2002:239944  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20020403  
Last Updated on STN: 20030506

AB Removal of L-**glutamate** (Glu) from the synapse is crit. to maintain normal transmission and to prevent excitotoxicity, and is performed exclusively by excitatory amino acid transporters (EAATs). We investigated the effects of substrates and blockers of EAATs on extracellular Glu and cellular viability in organotypic cultures of rat hippocampus. Seven-day treatment with a range of drugs (L-trans-pyrrolidine-2,4-dicarboxylate, (2S,4R)-4-methyl-**glutamate**, (1S,2S)-threo-3-methylglutamate and DL-threo-beta-benzyloxyaspartate), in the presence of 300  $\mu$ -M added Glu, resulted in increased extracellular Glu and a significant correlation between Glu concn. and cellular injury (as indicated by lactate dehydrogenase release). In contrast, (2S,3S,4R)-2-(carboxycyclopropyl)glycine (L-CCG-III) exerted a novel neuroprotection against this toxicity, and elevations in extracellular Glu were not toxic in the presence of this compd. Similar results were obtained following two-week treatment of cultures without added Glu. While blockade of GLT-1 alone was relatively ineffective in producing excitotoxic injury, heteroexchange of Glu by EAAT substrates may exacerbate excitotoxicity.

L84 ANSWER 22 OF 26 TOXCENTER COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 1999:176513 TOXCENTER  
COPYRIGHT: Copyright 2003 ACS  
DOCUMENT NUMBER: CA13118238280Q  
TITLE: Kainate receptors coupled to Gi/Go proteins in the rat hippocampus  
AUTHOR(S): Cunha, Rodrigo A.; Malva, Joao O.; Ribeiro, J. A.

CORPORATE SOURCE: Laboratory of Neurosciences, Faculty of Medicine and  
Department of Chemistry and Biochemistry, Faculty of  
Sciences, University of Lisbon, Port..

SOURCE: Molecular Pharmacology, (1999) Vol. 56, No. 2, pp.  
429-433.

CODEN: MOPMA3. ISSN: 0026-895X.

COUNTRY: PORTUGAL

DOCUMENT TYPE: Journal

FILE SEGMENT: CAPLUS

OTHER SOURCE: CAPLUS 1999:508729

LANGUAGE: English

ENTRY DATE: Entered STN: 20011116

Last Updated on STN: 20020509

AB Kainate receptors are a subtype of ionotropic **glutamate** receptors, permeable to cations and thus expected to have an excitatory depolarizing action on neurons. However, kainate receptor activation inhibits  $\gamma$ -aminobutyric acid release in the hippocampus through activation of protein kinase C in a pertussis toxin-dependent manner, suggesting a coupling of kainate receptors to G proteins. Thus, we directly investigated the G protein coupling of kainate receptors in the rat hippocampus by using a selective kainate receptor agonist, [3H](2S,4R)-4-methylglutamate ([3H]MGA). [3H]MGA bound to a single site to hippocampal membranes with a KD value of 32 nM and a Bmax value of 1024 fmol/mg protein. This binding likely represents kainate receptors because it was displaced by domoate ( $K_i = 4$  nM), kainate ( $K_i = 11$  nM), and 6-cyano-7-nitroquinoxaline-2,3-dione ( $K_i = 1.4$   $\mu$ M), but not by  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionate ( $K_i > 10$   $\mu$ M), (RS)- $\alpha$ -methyl-4-phosphonophenylglycine ( $K_i > 10$   $\mu$ M), or (+/-)-1-aminocyclopentane-trans-1,3-dicarboxylic acid ( $K_i > 10$   $\mu$ M). Guanylyl imidodiphosphate (30  $\mu$ M), which uncouples all G protein-coupled receptors, shifted to the right the satn. curve of [3H]MGA (KD = 133 nM). This effect was mimicked by pretreatment of hippocampal membranes with modifiers of Gi/Go proteins [30  $\mu$ M N-ethylmaleimide (KD = 98 nM) or 25  $\mu$ g/mL pertussis toxin (KD = 95 nM)] but not by a modifier of Gs proteins [50  $\mu$ g/mL cholera toxin (KD = 32 nM)]. Treatment of solubilized hippocampal membranes with pertussis toxin (25  $\mu$ g/mL) decreased [3H]MGA affinity (KD = 105-113 nM), which was recovered by reconstitution of these pretreated solubilized hippocampal membranes with Gi/Go proteins (KD = 41-76 nM). These results indicate that hippocampal kainate receptors are coupled to Gi/Go proteins.

L84 ANSWER 23 OF 26 TOXCENTER COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:168316 TOXCENTER

COPYRIGHT: Copyright 2003 ACS

DOCUMENT NUMBER: CA12505051027W

TITLE: Cytotoxic effects of kainate ligands on HEK cell lines  
expressing recombinant kainate receptors

AUTHOR(S): Carver, Jeffrey M.; Mansson, P.-Erik; Cortes-Burgos, Luz;  
Shu, Joanne; Zhou, Li Ming; Howe, James R.; Giordano, Tony

CORPORATE SOURCE: Symphony Pharmaceuticals, Inc., Department of Molecular  
Biology, Malvern, PA, 19355, USA.

SOURCE: Brain Research, (1996) Vol. 720, No. 1,2, pp. 69-74.

CODEN: BRREAP. ISSN: 0006-8993.

COUNTRY: UNITED STATES

DOCUMENT TYPE: Journal

FILE SEGMENT: CAPLUS

OTHER SOURCE: CAPLUS 1996:360038

LANGUAGE: English

ENTRY DATE: Entered STN: 20011116

Last Updated on STN: 20020730

AB Exposure of neurons either for prolonged periods of time or to high concns. of excitatory amino acids (EAA), such as **glutamate**, results in neuronal death. Kainate also causes cell toxicity through the

**glutamate** receptors. However, it is unclear whether the kainate receptor itself mediates any of the toxic responses. In the present study, HEK cells expressing the GluR6 .+-. KA2 receptor subunit(s) were studied for their susceptibility to toxicity through the kainate receptor by kainate ligands. The natural ligand, **glutamate**, did not result in toxicity to the recombinant cell lines over that obsd. with the untransfected HEK cells, whereas kainate produced a 2-3-fold increase in LDH in both the HEK/GluR6 and HEK/GluR6+KA2 cell lines following treatment with various dosages, but did not affect the HEK cells. Similar 2-3-fold increases in LDH activity were detected in both recombinant cell lines following treatment with 100 nM of SYM2081 ((2S,4R)-4-methylglutamic acid), a dose at which agonistic activity is elicited. The rank order potencies for eliciting toxicity are consistent with the previously reported EC50 values (SYM2081 > kainate >>> **glutamate**). Surprisingly, the kainate antagonist, NBQX, was the most toxic of the compds. tested although it had an affinity for the kainate receptor similar to **glutamate**. Treatment with as little as 10 nM elicited a dramatic increase in toxicity (6-10-fold) in the recombinant cell lines. At 1 .mu.M, NBQX was significantly more toxic (Fisher PLSD) than any of the other compds. tested. Thus, it appears that cell toxicity can be mediated via kainate receptor through two independent mechanisms: activation and blockage of the kainate receptor.

L84 ANSWER 24 OF 26 USPATFULL

ACCESSION NUMBER: 2002:330336 USPATFULL

TITLE: Methods for modulation, stimulation, and inhibition of glutamate reuptake

INVENTOR(S): Maccocchi, Maria-Luisa, West Chester, PA, UNITED STATES

Pei, Xue-Feng, Lansdale, PA, UNITED STATES

PATENT ASSIGNEE(S): Annovis. Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002188022	A1	20021212
APPLICATION INFO.:	US 2001-21177	A1	20011030 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-244252P	20001030 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400	

NUMBER OF CLAIMS: 9  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 13 Drawing Page(s)  
LINE COUNT: 1053

CAS INDEXING IS AVAILABLE FOR THIS PATENT

AB Disclosed is a method for inhibiting, stimulating, modulating, or regulating glutamate reuptake. The method makes use of compounds that are ligands of glutamate receptors, including many agonists, or antagonists of glutamate receptors. It has been discovered that such compounds can bind to or modulate glutamate transporters and affect extracellular glutamate levels by affecting transporter activity. The disclosed compounds can have a variety of effects on glutamate transporter activity including activation or inhibition. Such compounds are useful to treat various neurological diseases and conditions involving glutamate transporter and glutamate receptor activation. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporters can ameliorate excessive activation of glutamate

receptors by reducing the extracellular glutamate concentration. Prodrug forms of transporter compounds can be used as drugs.

IT 31137-74-3, SYM 2081

(glutamate receptor ligands for modulation, stimulation, and inhibition of glutamate transport)

L84 ANSWER 25 OF 26 USPATFULL

ACCESSION NUMBER: 2002:214299 USPATFULL

TITLE: Screen for glutamate reuptake inhibitors, stimulators, and modulators

INVENTOR(S): Beart, Philip M., Ivanhoe, AUSTRALIA  
O'Shea, Ross D., Blackburn South, AUSTRALIA  
Aprico, Karina, Forest Hill, AUSTRALIA  
Lawrence, Andrew J., Brighton, AUSTRALIA  
Maccecchini, Maria-Luisa, West Chester, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002115688	A1	20020822
APPLICATION INFO.:	US 2001-944954	A1	20010901 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-229952P	20000901 (60)
	US 2000-230159P	20000901 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400

NUMBER OF CLAIMS: 27

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 14 Drawing Page(s)

LINE COUNT: 1184

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method for identifying compounds that bind to or modulate a glutamate transporter. The disclosed method is useful for identifying compounds that can inhibit, stimulate, or modulate the activity of the glutamate transporter and thus affect glutamate reuptake. The method is a screening technique where compounds known to bind to glutamate receptors (for example, glutamate receptor ligands, including many agonists, and antagonists) are bound to a glutamate transporter and compounds are screened to identify those that can alter the binding of the glutamate receptor-binding compounds. Compounds shown to alter the binding of the receptor compounds from glutamate transporters in the disclosed assay can have a variety of effects on glutamate transporter activity including activation or inhibition. These compounds are expected to affect or interfere with glutamate reuptake by the glutamate transporter and thus can be used to modulate, stimulate, or inhibit glutamate reuptake. Such compounds are useful to treat various neurological diseases and conditions involving glutamate transporter and glutamate receptor activation. One of the compounds is (2S,4R)-4-methylglutamate or [<sup>sup</sup>.3H]-(2S,4R)-4-methylglutamate. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate reuptake by glutamate transporters can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concentration. Prodrug forms of transporter compounds are preferred for use as drugs.

IT 31137-74-3

(screening for glutamate reuptake inhibitors, stimulators, and modulators)

*dupl*

L84 ANSWER 26 OF 26 USPATFULL

ACCESSION NUMBER: 1998:31053 USPATFULL

TITLE: Alkylcarboxy amino acids-modulators of the kainate receptor

INVENTOR(S): Gu, Zi-Qiang, Rosemont, PA, United States

PATENT ASSIGNEE(S): Bearsden Bio, Inc., Philadelphia, PA, United States  
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5731348		19980324
APPLICATION INFO.:	US 1996-600330		19960213 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1995-389916, filed on 15 Feb 1995, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Jarvis, William R. A.		
LEGAL REPRESENTATIVE:	Arnall, Golden & Gregory, LLP		
NUMBER OF CLAIMS:	6		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 3 Drawing Page(s)		
LINE COUNT:	1243		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds of a new class of alkyl carboxy amino acid analogs of glutamic acid act as specific regulators of the kainic acid EAA receptor cation channel. These compounds are useful for treating neurological, neuropsychological, neuropsychiatric, neurodegenerative, neuropsychopharmacological and functional disorders associated with excessive or insufficient activation of the kainic acid subtype of the ionotropic EAA receptors; treating cognitive disorders associated with deactivation, suboptimal activation or over-activation of the kainic acid receptor; alleviating pain and improving and enhancing memory, learning, and associated mental processes. A method for designing novel AMPA or kainic acid receptor agonists or antagonists is also disclosed.

IT 31137-74-3P

(prepn. of carboxyalkyl amino acids as modulators of the kainate receptor)

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=> fil medl drugu embase wpids scisearch  
FILE 'MEDLINE' ENTERED AT 12:03:30 ON 25 JUN 2003

FILE 'DRUGU' ENTERED AT 12:03:30 ON 25 JUN 2003  
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*text  
search*

=> d que 175; d que 180; s 175 or 180  
L68 74 SEA SYM(W) (2081 OR 2083 OR 2062 OR 2051)  
L69 12 SEA SYM2081 OR SYM2083 OR SYM2062 OR SYM2051  
L70 1 SEA LY310214 OR LY 310214  
L71 9 SEA ERYTHRO(2A) (METHYLGLUTAM? OR METHYL(2A) GLUTAM?)  
L72 206656 SEA GLUTAMATE OR GLUTAMIC ACID  
L73 508158 SEA UPTAK? OR REUPTAK?  
L74 6921 SEA L72(3A) LEVEL#  
L75 4 SEA (L68 OR L69 OR L70 OR L71) AND ((L72 AND L73) OR L74)

L68 74 SEA SYM(W) (2081 OR 2083 OR 2062 OR 2051)  
L69 12 SEA SYM2081 OR SYM2083 OR SYM2062 OR SYM2051  
L70 1 SEA LY310214 OR LY 310214  
L71 9 SEA ERYTHRO(2A) (METHYLGLUTAM? OR METHYL(2A) GLUTAM?)  
L72 206656 SEA GLUTAMATE OR GLUTAMIC ACID  
L76 70 SEA (L68 OR L69 OR L70 OR L71) AND L72  
L77 3096538 SEA BRAIN OR NERVE# OR NEURON? OR NERVOUS SYSTEM  
L79 228690 SEA L77(5A) (DISEASE# OR DISORDER# OR DYSFUNCTION?)  
L80 4 SEA L76 AND L79

L81 8 L75 OR L80

=> dup rem l81  
PROCESSING COMPLETED FOR L81  
L82 4 DUP REM L81 (4 DUPLICATES REMOVED)  
ANSWERS '1-2' FROM FILE MEDLINE  
ANSWER '3' FROM FILE DRUGU  
ANSWER '4' FROM FILE EMBASE

=> d iall 1-4; fil hom

L82 ANSWER 1 OF 4 MEDLINE DUPLICATE 1  
ACCESSION NUMBER: 1998260314 MEDLINE  
DOCUMENT NUMBER: 98260314 PubMed ID: 9580595  
TITLE: The methylglutamate, **SYM 2081**, is a  
potent and highly selective agonist at kainate receptors.  
AUTHOR: Donevan S D; Beg A; Gunther J M; Twyman R E  
CORPORATE SOURCE: Department of Neurology, University of Utah, Salt Lake  
City, USA.  
CONTRACT NUMBER: NS31519 (NINDS)  
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,  
(1998 May) 285 (2) 539-45.  
Journal code: 0376362. ISSN: 0022-3565.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199806  
ENTRY DATE: Entered STN: 19980618  
Last Updated on STN: 19980618  
Entered Medline: 19980608

## ABSTRACT:

The methylglutamate analog (2S,4R)-4-methylglutamate (**SYM 2081**) has been shown to potently displace high affinity [3H]kainate binding to cortical tissue and to recombinant kainate receptors, and to evoke rapidly desensitizing responses in electrophysiological recordings. We have used two electrode voltage clamp recordings to compare the potency and efficacy of **SYM 2081** with other alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA)/kainate receptor agonists at homomeric kainate and AMPA receptors expressed in *Xenopus* oocytes. In the presence of concanavalin A to reduce agonist induced desensitization at kainate receptors, **SYM 2081** was a potent agonist at homomeric kainate receptors composed of the GluR5 and GluR6 subunit, with an EC<sub>50</sub> of 0.12 +/- 0.02 and 0.23 +/- 0.01 microM, respectively. **SYM 2081** was highly selective for kainate receptors, the EC<sub>50</sub> for activation of AMPA receptors composed of the GluR1 and GluR3 subunits was 132 +/- 44 and 453 +/- 57 microM, respectively. Other methylglutamate analogs were tested for kainate receptor agonist activity. Methylglutamate compounds with the methyl group at the 2 or 3 position of **glutamate** were inactive indicating that positioning of the methyl group at the 4 position was essential for agonist activity. Of the four stereoisomers of 4-methylglutamate, **SYM 2081** (2S,4R) was the most potent agonist. The (2R,4R) isomer was estimated to be 20-fold and the (2S,4S)-isomer approximately 1000-fold less potent than **SYM 2081**. These results indicate that **SYM 2081** is a potent and selective agonist at kainate receptors, and thus will be a useful ligand for evaluating the role of kainate receptors in central nervous system function and disease.

CONTROLLED TERM: Check Tags: Animal; Female; Support, Non-U.S. Gov't;  
Support, U.S. Gov't, P.H.S.

\*Glutamates: PD, pharmacology  
Receptors, AMPA: DE, drug effects  
\*Receptors, Kainic Acid: AG, agonists  
Receptors, Kainic Acid: PH, physiology  
Stereoisomerism  
Structure-Activity Relationship  
*Xenopus*

CAS REGISTRY NO.: 14561-55-8 (4-methylglutamic acid)  
CHEMICAL NAME: 0 (Glutamates); 0 (Receptors, AMPA); 0 (Receptors, Kainic Acid)

L82 ANSWER 2 OF 4

MEDLINE

DUPLICATE 2

ACCESSION NUMBER: 93218798 MEDLINE

DOCUMENT NUMBER: 93218798 PubMed ID: 8096630

TITLE: **Glutamate uptake** system in the presynaptic vesicle: **glutamic acid** analogs as inhibitors and alternate substrates.

AUTHOR: Winter H C; Ueda T

CORPORATE SOURCE: Department of Biological Chemistry, Medical School, University of Michigan, Ann Arbor 48109.

CONTRACT NUMBER: NS 026107 (NINDS)

SOURCE: NEUROCHEMICAL RESEARCH, (1993 Jan) 18 (1) 79-85.  
Journal code: 7613461. ISSN: 0364-3190.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199305  
ENTRY DATE: Entered STN: 19930521  
Last Updated on STN: 20000303  
Entered Medline: 19930506

## ABSTRACT:

A variety of naturally occurring amino acids, their isomers, and synthetic analogs were tested for their ability to inhibit **uptake** of [3H] **\*\*\*glutamate\*\*\*** into presynaptic vesicles from bovine cerebral cortex. Strongest inhibition ( $K_i < 1\text{mM}$ ) was observed for trans-1-aminocyclopentane-1,3-dicarboxylic acid (t-ACPD) and **erythro-4-methyl-L-\*\*\*glutamic\*\*\* acid** (MGLu), while 4-methylene-L-**glutamic acid** (MeGlu) was only moderately inhibitory ( $K_i = \text{approximately } 3\text{mM}$ ), indicating that the synaptic vesicle **glutamate** translocator has higher affinity for trans-ACPD and MGLu than for **glutamate**. A few other amino acids, e.g., 4-hydroxyglutamic acid, S-carboxyethyl cysteine, and 5-fluorotryptophan, were slightly inhibitory; all L- and DL-isomers of protein amino acids and longer chain acidic amino acids were without measurable inhibition. Potassium tetrathionate and S-sulfocysteine exhibited strong to moderate noncompetitive or irreversible inhibition. Inhibition by t-ACPD, MGLu, or MeGlu was competitive with **glutamic acid**. Each of these competitive inhibitors was also taken up by the vesicle preparation in an ATP-dependent manner, as indicated by their being recovered unchanged from filtered vesicles. Similar results were obtained with reconstituted vesicles, while **glutamate uptake** by partially purified rat synaptosomes was inhibited only by MGLu. These results indicate that the **\*\*\*glutamate\*\*\*** translocator of presynaptic vesicles has stringent structural requirements distinct from those of the plasma membrane translocator and the metabotropic type of postsynaptic **glutamate** receptor. They further suggest possible structural requirements of pharmacologically significant compounds that can substitute for **glutamic acid** in the presynaptic side of glutamatergic synapses, thus serving to moderate or control **\*\*\*glutamate\*\*\*** excitation and associated excitotoxic effects in these neurons.

CONTROLLED TERM: Check Tags: Animal; Support, U.S. Gov't, P.H.S.  
Cattle  
\*Cerebral Cortex: ME, metabolism  
Cycloleucine: AA, analogs & derivatives  
Cycloleucine: ME, metabolism  
Cycloleucine: PD, pharmacology  
Cysteine: AA, analogs & derivatives  
Cysteine: PD, pharmacology  
\*Glutamates: ME, metabolism  
\*Glutamates: PD, pharmacology  
**Glutamic Acid**  
Synaptic Vesicles: DE, drug effects  
\*Synaptic Vesicles: ME, metabolism  
Tryptophan: AA, analogs & derivatives  
Tryptophan: PD, pharmacology  
CAS REGISTRY NO.: 111900-32-4 (1-amino-1,3-dicarboxycyclopentane); 14561-55-8 (4-methylglutamic acid); 1637-71-4 (S-sulphocysteine); 343-91-9 (5-fluorotryptophan); 52-52-8 (Cycloleucine); 52-90-4 (Cysteine); **56-86-0 (Glutamic Acid)**; 7150-74-5 (4-methyleneglutamic acid); 73-22-3 (Tryptophan)  
CHEMICAL NAME: 0 (Glutamates)

L82 ANSWER 3 OF 4 DRUGU COPYRIGHT 2003 THOMSON DERWENT

ACCESSION NUMBER: 1998-12102 DRUGU P

TITLE: A novel kainate receptor ligand (3H)-(2S,4R)-4-methylglutamate: pharmacological characterization in rabbit brain membranes.

AUTHOR: Toms N J; Reid M E; Phillips W; Kemp M C; Roberts P J

CORPORATE SOURCE: Univ.Bristol; Tocris-Cookson

LOCATION: Bristol, U.K.

SOURCE: Neuropharmacology (36, No. 11-12, 1483-88, 1997) 4 Fig. 1  
Tab. 21 Ref.

CODEN: NEPHBW ISSN: 0028-3908

AVAIL. OF DOC.: Department of Pharmacology, School of Medical Sciences,  
University of Bristol, University Walk, Bristol BS8 1TD,  
England. (email: P.J.Roberts@bristol.ac.uk). (P.J.R.).

LANGUAGE: English

DOCUMENT TYPE: Journal

ABSTRACT:

In rabbit whole brain membranes in-vitro, 3H-(2S,4R)-4-methylglutamate (MG, \*\*\*SYM\*\*\* -2081) bound to 2 sites. Characterization with antagonists indicated that MG was a useful ligand for labelling kainate receptors, with high selectivity and a pharmacology similar to that for rat cloned low affinity (Glu5 and 6) kainate receptor subunits.

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 60 Autonomic  
63 Receptors  
73 Trial Preparations

CONTROLLED TERM:

[01]

**SYM-2081** \*PH; KAINATE \*RC;  
**GLUTAMATE** \*RC; DOMOATE \*RC; QUISQUALATE \*RC; FG-9065  
\*RC; AMPA \*RC; FLUOROWILLARDIINE \*RC; METHYLASPARTATE-N \*RC;  
NS-102 \*RC; AMINOPHOSPHONOBUTANOATE \*RC; DR9505061 \*RN;  
IN-VITRO \*FT; RABBIT \*FT; BRAIN \*FT; MEMBRANE \*FT;  
KAINATE-RECEPTOR \*FT; BINDING \*FT; CHARACTERIZATION \*FT;  
TRITIUM-LABELED \*FT; AFFINITY \*FT; LAB.ANIMAL \*FT;  
SUBCELL.STRUCT. \*FT; RECEPTOR \*FT; **GLUTAMATE**  
-RECEPTOR \*FT; TRIAL-PREP. \*FT; PH \*FT

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

L82 ANSWER 4 OF 4 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999049700 EMBASE

TITLE: Society for Neuroscience - 28th Annual Meeting:  
**Glutamate** receptors.

AUTHOR: Salt T.

CORPORATE SOURCE: T. Salt, Department of Visual Science, Institute of  
Ophthalmology, University College London, 11-43 Bath  
Street, London EC1V 9EL, United Kingdom. T.SALT@UCLAC.UK

SOURCE: IDrugs, (1999) 2/1 (1-3).  
ISSN: 1369-7056 CODEN: IDRUFN

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 008 Neurology and Neurosurgery  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT:

This meeting, stretching over 5 days with approximately 24,000 registrants, had approximately 13,000 oral and poster presentations covering all areas of neuroscience. This review focuses on a selection of new developments in the field of **glutamate** receptors. This area is receiving considerable attention from research groups in both academic and industrial establishments, and it is notable that many efforts are collaborative between workers from these different types of establishment. **Glutamate** receptors (GluR) can be classified as ionotropic (iGluR) or metabotropic (mGluR) receptors. Amongst the ionotropic receptors are the NMDA receptors, AMPA receptors and

kainate receptors, whilst there are eight subtypes of mGluRs which can be placed into three groups on the basis of sequence homology, pharmacology and intracellular transduction mechanism.

CONTROLLED TERM: Medical Descriptors:

**\*brain disease**

\*drug mechanism

brain protection

epilepsy

analgesia

nerve degeneration

protein domain

brain infarction

cognitive defect

neurotoxicity

human

nonhuman

mouse

animal experiment

controlled study

human cell

animal cell

conference paper

Drug Descriptors:

**\*glutamate receptor**

\*ionotropic receptor

\*cp 465022: DV, drug development

\*2 (3 carboxybicyclo[1.1.1]pentyl)glycine: DV, drug development

\*rpr 118723: DV, drug development

\*ly 393675: DV, drug development

quisqualic acid receptor

n methyl dextro aspartic acid receptor

kainic acid receptor

1 (4 aminophenyl) 3,4 dihydro 4 methyl 3 methylcarbamoyl

7,8 methylenedioxy 5h 2,3 benzodiazepine

decahydro 6 [2 (1h tetrazol 5 yl)ethyl] 3

isoquinolinecarboxylic acid

4 methylglutamic acid

ly 379268: DV, drug development

**glutamate receptor agonist: DV, drug development**

AMPA receptor antagonist: DV, drug development

**glutamic acid antagonist: DV, drug development**

cgp 68730a: DV, drug development

upf 596

CAS REGISTRY NO.: (1 (4 aminophenyl) 3,4 dihydro 4 methyl 3 methylcarbamoyl 7,8 methylenedioxy 5h 2,3 benzodiazepine) 143692-48-2; (decahydro 6 [2 (1h tetrazol 5 yl)ethyl] 3 isoquinolinecarboxylic acid) 154652-83-2; (4 methylglutamic acid) 14561-55-8

CHEMICAL NAME: (1) Ly 293558; (2) Gyki 53655; (3) **Sym 2081**; (4) Ly 393675; (5) Cp 465022; (6) Rpr 118723; (7) Ly 379268; (8) Cgp 68730a; Upf 596

COMPANY NAME: (2) Egis gyogyszergyar; (3) Symphony; (5) Pfizer; (6) Rhone Poulenc Rorer; (7) Lilly; (8) Novartis

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FILE COVERS 1907 - 25 Jun 2003 VOL 138 ISS 26

FILE LAST UPDATED: 24 Jun 2003 (20030624/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

*inventor  
search*

L1 41 SEA FILE=CAPLUS ABB=ON MACCECCHINI M?/AU  
L2 257 SEA FILE=CAPLUS ABB=ON PEI X?/AU  
L3 7 SEA FILE=CAPLUS ABB=ON L1 AND L2

L1 41 SEA FILE=CAPLUS ABB=ON MACCECCHINI M?/AU  
L2 257 SEA FILE=CAPLUS ABB=ON PEI X?/AU  
L5 11863 SEA FILE=CAPLUS ABB=ON GLUTAMATE RECEPTORS/CT  
L8 256906 SEA FILE=CAPLUS ABB=ON ?UPTAKE?  
L9 1 SEA FILE=CAPLUS ABB=ON (L1 OR L2) AND L5 AND L8

L50 7 L3 OR L9

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FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 19 June 2003 (20030619/ED)

L33 34 SEA FILE=BIOSIS ABB=ON MACCECCHINI M?/AU  
L34 144 SEA FILE=BIOSIS ABB=ON PEI X?/AU  
L36 4 SEA FILE=BIOSIS ABB=ON L33 AND L34

L31 72397 SEA FILE=BIOSIS ABB=ON GLUTAMATE#  
L33 34 SEA FILE=BIOSIS ABB=ON MACCECCHINI M?/AU

L34 144 SEA FILE=BIOSIS ABB=ON PEI X?/AU  
L37 4 SEA FILE=BIOSIS ABB=ON (L33 OR L34) AND L31

L51 7 L36 OR L37

=> fil toxcenter; d que 143; d que 146; d que 148; s 143 or 146 or 148  
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TOXCENTER has been enhanced with new files segments and search fields.  
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the  
MeSH 2003 vocabulary. See <http://www.nlm.nih.gov/mesh/summ2003.html>  
for a description on changes.

L41 17 SEA FILE=TOXCENTER ABB=ON MACCECCHINI M?/AU  
L42 83 SEA FILE=TOXCENTER ABB=ON PEI X?/AU  
L43 1 SEA FILE=TOXCENTER ABB=ON L41 AND L42

L39 39154 SEA FILE=TOXCENTER ABB=ON GLUTAMATE#  
L41 17 SEA FILE=TOXCENTER ABB=ON MACCECCHINI M?/AU  
L42 83 SEA FILE=TOXCENTER ABB=ON PEI X?/AU  
L45 117819 SEA FILE=TOXCENTER ABB=ON REUPTAK? OR UPTAK?  
L46 1 SEA FILE=TOXCENTER ABB=ON (L41 OR L42) AND L39 AND L45

L39 39154 SEA FILE=TOXCENTER ABB=ON GLUTAMATE#  
L41 17 SEA FILE=TOXCENTER ABB=ON MACCECCHINI M?/AU  
L42 83 SEA FILE=TOXCENTER ABB=ON PEI X?/AU  
L47 1877 SEA FILE=TOXCENTER ABB=ON L39(3A)LEVEL#  
L48 1 SEA FILE=TOXCENTER ABB=ON L47 AND (L41 OR L42)

L52 1 L43 OR L46 OR L48

=> fil medl; d que 155;d que 157  
FILE 'MEDLINE' ENTERED AT 11:57:01 ON 25 JUN 2003

FILE LAST UPDATED: 24 JUN 2003 (20030624/UP). FILE COVERS 1958 TO DATE.

On April 13, 2003, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the  
MeSH 2003 vocabulary. See <http://www.nlm.nih.gov/mesh/changes2003.html>  
for a description on changes.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.



L53 16 SEA FILE=MEDLINE ABB=ON MACCECCHINI M?/AU  
L54 135 SEA FILE=MEDLINE ABB=ON PEI X?/AU  
L55 1 SEA FILE=MEDLINE ABB=ON L53 AND L54

L53 16 SEA FILE=MEDLINE ABB=ON MACCECCHINI M?/AU  
L54 135 SEA FILE=MEDLINE ABB=ON PEI X?/AU  
L56 16750 SEA FILE=MEDLINE ABB=ON GLUTAMIC ACID/CT  
L57 2 SEA FILE=MEDLINE ABB=ON (L53 OR L54) AND L56

=> s l55 or l57

L65 3 L55 OR L57

=> fil embase; d que l60; d que l64; s l60 or l64

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FILE COVERS 1974 TO 19 Jun 2003 (20030619/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

L58 13 SEA FILE=EMBASE ABB=ON MACCECCHINI M?/AU  
L59 89 SEA FILE=EMBASE ABB=ON PEI X?/AU  
L60 1 SEA FILE=EMBASE ABB=ON L58 AND L59

L58 13 SEA FILE=EMBASE ABB=ON MACCECCHINI M?/AU  
L59 89 SEA FILE=EMBASE ABB=ON PEI X?/AU  
L61 27232 SEA FILE=EMBASE ABB=ON GLUTAMIC ACID/CT  
L62 2 SEA FILE=EMBASE ABB=ON GLUTAMATE UPTAKE INHIBITOR/CT  
L64 2 SEA FILE=EMBASE ABB=ON (L58 OR L59) AND (L61 OR L62)

L66 3 L60 OR L64

=> dup rem l65,l50,l51,l66,l52

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PROCESSING COMPLETED FOR L65

PROCESSING COMPLETED FOR L50

PROCESSING COMPLETED FOR L51

PROCESSING COMPLETED FOR L66

PROCESSING COMPLETED FOR L52

L67 13 DUP REM L65 L50 L51 L66 L52 (8 DUPLICATES REMOVED)  
ANSWERS '1-3' FROM FILE MEDLINE  
ANSWERS '4-9' FROM FILE CAPLUS  
ANSWERS '10-13' FROM FILE BIOSIS

=&gt; d ibib ab 1-13

L67 ANSWER 1 OF 13 MEDLINE DUPLICATE 2  
ACCESSION NUMBER: 2001563541 MEDLINE  
DOCUMENT NUMBER: 21521563 PubMed ID: 11640930  
TITLE: Point mutations identify the glutamate binding pocket of the N-methyl-D-aspartate receptor as major site of conantokin-G inhibition.  
AUTHOR: Wittekindt B; Malany S; Schemm R; Otvos L; **Maccacchini M L**; Laube B; Betz H  
CORPORATE SOURCE: Department of Neurochemistry, Max-Planck-Institute for Brain Research, Deutschordenstrasse 46, 60528, Frankfurt/Main, Germany.  
SOURCE: NEUROPHARMACOLOGY, (2001 Nov) 41 (6) 753-61.  
Journal code: 0236217. ISSN: 0028-3908.  
PUB. COUNTRY: England: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200201  
ENTRY DATE: Entered STN: 20011022  
Last Updated on STN: 20020125  
Entered Medline: 20020110

AB Conantokin-G (Con-G), a gamma-carboxylglutamate (Gla) containing peptide derived from the venom of the marine cone snail *Conus geographus*, acts as a selective and potent inhibitor of N-methyl-D-aspartate (NMDA) receptors. Here, the effect of Con-G on recombinant NMDA receptors carrying point mutations within the glycine and glutamate binding pockets of the NR1 and NR2B subunits was studied using whole-cell voltage-clamp recording from cRNA injected *Xenopus* oocytes. At wild-type receptors, glutamate-induced currents were inhibited by Con-G in a dose-dependent manner at concentrations of 0.1-100 microm. Substitution of selected residues within the NR2B subunit reduced the inhibitory potency of Con-G, whereas similar mutations in the NR1 subunit had little effect. These results indicate a selective interaction of Con-G with the glutamate binding pocket of the NMDA receptor. Homology-based molecular modeling of the glutamate binding region based on the known structure of the glutamate binding site of the AMPA receptor protein GluR2 suggests how selected amino acid side chains of NR2B might interact with specific residues of Con-G.

L67 ANSWER 2 OF 13 MEDLINE DUPLICATE 4  
ACCESSION NUMBER: 1999196294 MEDLINE  
DOCUMENT NUMBER: 99196294 PubMed ID: 10098658  
TITLE: Allosteric modulators of the AMPA receptor: novel 6-substituted dihydrophthalazines.  
AUTHOR: **Pei X F**; Sturgess M A; Valenzuela C F; **Maccacchini M L**  
CORPORATE SOURCE: Bearsden Bio, Inc., Aston, PA 19014, USA.  
SOURCE: BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, (1999 Feb 22) 9 (4) 539-42.  
Journal code: 9107377. ISSN: 0960-894X.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199905  
ENTRY DATE: Entered STN: 19990607  
Last Updated on STN: 19990607  
Entered Medline: 19990524

AB Novel analogs of the allosteric AMPA receptor modulator SYM 2206 have been prepared. Structure/activity correlations of these novel analogs and other dihydrophthalazines (DHPs) reveal the important contribution of the heteroatom-based aryl substituents in this class of noncompetitive inhibitors. One of the analogs (6, SYM 2189) is equipotent with the early series, but with reduced sedation.

L67 ANSWER 3 OF 13 MEDLINE

ACCESSION NUMBER: 2000270252 MEDLINE

DOCUMENT NUMBER: 20270252 PubMed ID: 10809774

TITLE: The conformational activation of antithrombin. A 2.85-A structure of a fluorescein derivative reveals an electrostatic link between the hinge and heparin binding regions.

AUTHOR: Huntington J A; McCoy A; Belzar K J; **Pei X Y**;  
Gettins P G; Carrell R W

CORPORATE SOURCE: University of Cambridge, Department of Haematology,  
Wellcome Trust Centre for the Study of Molecular Mechanisms  
in Disease, Cambridge Institute for Medical Research, Hills  
Road, Cambridge CB2 2XY, United Kingdom.. jah52@cam.ac.uk

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 May 19) 275 (20)  
15377-83.

Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: PDB-1DZG; PDB-1DZH

ENTRY MONTH: 200006

ENTRY DATE: Entered STN: 20000629

Last Updated on STN: 20000629

Entered Medline: 20000621

AB Antithrombin is unique among the serpins in that it circulates in a native conformation that is kinetically inactive toward its target proteinase, factor Xa. Activation occurs upon binding of a specific pentasaccharide sequence found in heparin that results in a rearrangement of the reactive center loop removing constraints on the active center P1 residue. We determined the crystal structure of an activated antithrombin variant, N135Q S380C-fluorescein (P14-fluorescein), in order to see how full activation is achieved in the absence of heparin and how the structural effects of the substitution in the hinge region are translated to the heparin binding region. The crystal structure resembles native antithrombin except in the hinge and heparin binding regions. The absence of global conformational change allows for identification of specific interactions, centered on Glu(381) (P13), that are responsible for maintenance of the solution equilibrium between the native and activated forms and establishes the existence of an electrostatic link between the hinge region and the heparin binding region. A revised model for the mechanism of the allosteric activation of antithrombin is proposed.

L67 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1

ACCESSION NUMBER: 2002:391517 CAPLUS

DOCUMENT NUMBER: 136:395975

TITLE: Glutamate receptor ligands for modulation,  
stimulation, and inhibition of glutamate transport

INVENTOR(S): **Maccacchini, Maria-Luisa; Pei,**  
**Xue-Feng**

PATENT ASSIGNEE(S): Annovis, Inc., USA

SOURCE: PCT Int. Appl., 48 pp.

CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002040002	A2	20020523	WO 2001-US48448	20011030
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2002037717	A5	20020527	AU 2002-37717	20011030
US 2002188022	A1	20021212	US 2001-21177	20011030
PRIORITY APPLN. INFO.:			US 2000-244252P P	20001030
			WO 2001-US48448 W	20011030

OTHER SOURCE(S): MARPAT 136:395975

AB The invention discloses the use of glutamate receptor ligands (agonists and antagonists) for inhibiting, stimulating, modulating, or regulating glutamate **reuptake**. It has been discovered that such compds. can bind to or modulate glutamate transporters and affect extracellular glutamate levels by affecting transporter activity. The disclosed compds. can have a variety of effects on glutamate transporter activity including activation or inhibition. Such compds. are useful to treat various neurol. diseases and conditions involving glutamate transporter and glutamate receptor activation. For example, excess extracellular glutamate is a cause of excessive activation of glutamate receptors. Stimulating glutamate **reuptake** by glutamate transporters can ameliorate excessive activation of glutamate receptors by reducing the extracellular glutamate concn. Prodrug forms of transporter compds. can be used as drugs.

L67 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3  
ACCESSION NUMBER: 2001:640039 CAPLUS  
TITLE: Novel 5H-2,3-benzodiazepine antagonists of AMPA receptors  
AUTHOR(S): Pei, Xue-Feng; Li, Baoqing; Macccecchini, Maria  
CORPORATE SOURCE: Department of Medicinal Chemistry, Annovis, Inc, Aston, PA, 19014, USA  
SOURCE: Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001 (2001), MEDI-220. American Chemical Society: Washington, D. C.  
CODEN: 69BUZP  
DOCUMENT TYPE: Conference; Meeting Abstract  
LANGUAGE: English

AB Excitatory neuronal transmission within the central nervous system is mediated predominately by ion flux through ion channels gated by glutamate. There are three major glutamate receptor subtypes: the N-methyl-D-aspartate (NMDA), 2S-amino-2-(5'-methyl-3'-hydroxyisoxazoline)-propionic acid (AMPA), and kainic acid (KA) receptor. Compds. that inhibit AMPA receptors have been shown to be effective neuroprotectants and have potential to treat epilepsy. We disclosed a series of dihydrophthalazine (1-3) as noncompetitive AMPA receptor antagonists (J. Med. Chem. 1996, 39, 343 and Bioorg. Med. Chem. Lett., 1999, 9, 539). It was also found that GYKI 53655 (4), a 5H-2,3-benzodiazepine, is a

noncompetitive AMPA receptor antagonist. We now report synthesis of novel 5H-2,3-benzodiazepines (5-8), and their anticonvulsant activities.

L67 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:539642 CAPLUS

DOCUMENT NUMBER: 137:94003

TITLE: Preparation of esters of carbalkoxy amino acids as prodrugs of modulators of the kainate receptor

INVENTOR(S): **Pei, Xue-Feng; Maccacchini, Maria-Luisa**

PATENT ASSIGNEE(S): Annovis, Inc., USA

SOURCE: PCT Int. Appl., 31 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002055479	A2	20020718	WO 2001-US48579	20011030
WO 2002055479	A3	20021024		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002115721	A1	20020822	US 2001-20842	20011030
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PRIORITY APPLN. INFO.: US 2000-244411P P 20001030

OTHER SOURCE(S): MARPAT 137:94003

AB Title compds. R5O2CCR1R2CH2CH(NR3R4)CO2R6 [R1, R2, R5, R6 = C1-C6-alkyl, C3-C4-alkenyl, C3-C5-cycloalkyl; R3, R4 = H, any group given for R1, C1-C6-alkyl-CO, C1-C6-alkyl-O2C or -NHCO, HCO, or C3-C6-alkynyl; R3 and R4 taken together can be CH2(CH2)nCH2, where n = 0-3] or their pharmaceutically acceptable salts were prepd. as specific regulators of the kainate excitatory amino acid receptor cation channel. These compds. are useful for treating neurol. and cognitive disorders, alleviating pain, and improving and enhancing mental processes. Thus, (2S,4R)-4-methylglutamic acid di-Me ester, prepd. by esterification of the acid, prevented hyperalgesia in the rat at 10 mg/kg.

L67 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:935585 CAPLUS

DOCUMENT NUMBER: 136:69827

TITLE: Preparation of 7- or 8-mono-substituted 5H-2,3-benzodiazepines as antagonists of excitatory amino acid receptors

INVENTOR(S): **Pei, Xue-Feng; Li, Baoqing; Maccacchini, Maria-Luisa**

PATENT ASSIGNEE(S): Annovis, Inc., USA

SOURCE: PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2001098280 A2 20011227 WO 2001-US19136 20010615  
WO 2001098280 A3 20020530

W: CA, JP

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
PT, SE, TR

US 2002025958 A1 20020228 US 2001-882843 20010615

EP 1296960 A2 20030402 EP 2001-948367 20010615

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:

US 2000-212238P P 20000616

WO 2001-US19136 W 20010615

OTHER SOURCE(S): MARPAT 136:69827

AB Title compds. [I; dotted bond = single, double; X = N, NR; R = COCH<sub>3</sub>, CONHCH<sub>3</sub>, CONHCH<sub>2</sub>CH<sub>3</sub>, CONHCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, CONHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; R<sub>2</sub> = H, OCH<sub>3</sub>, NH<sub>2</sub>, SCH<sub>3</sub>; R<sub>3</sub> = OCH<sub>3</sub>, H, NH<sub>2</sub>, SCH<sub>3</sub>] and pharmaceutically acceptable salts are prep'd. as active non-NMDA inotropic excitatory amino acid (EAA) receptor antagonists and are useful for treating disorders assoc'd. with excessive activation of the non-NMDA subtype of the inotropic EAA receptor. Title compds. I further are useful as testing agents to identify and characterize other compds. for the treatment of these disorders. The compds. are useful therapeutically as sedatives or for the treatment of neurosychopharmacol. disorders such as stroke, ischemia and epilepsy. The compns. may be provided in combination with a suitable carrier for oral or parenteral administration. The compds. may be administered orally or parenterally for the treatment of a variety of disorders assoc'd. with non-NMDA EAA receptor function.

L67 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:780863 CAPLUS

DOCUMENT NUMBER: 135:318511

TITLE: Preparation of aminophenylphthalazines as non-NMDA ionotropic excitatory amino acid receptor antagonists.

INVENTOR(S): Pei, Xue-Feng; Li, Baoqing;

Maccicchini, Maria-Luisa

PATENT ASSIGNEE(S): ANNOVIS, Inc., USA

SOURCE: PCT Int. Appl., 42 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001079181	A2	20011025	WO 2001-US11948	20010412
WO 2001079181	A3	20020321		

W: JP, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
PT, SE, TR

US 2002006925 A1 20020117 US 2001-833855 20010412

EP 1274689 A2 20030115 EP 2001-969042 20010412

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, FI, CY, TR

PRIORITY APPLN. INFO.:

US 2000-196823P P 20000413

WO 2001-US11948 W 20010412

OTHER SOURCE(S): MARPAT 135:318511

AB Title compds. [I; R<sub>1</sub>-R<sub>4</sub> = H, OH, R<sub>10</sub>, halo, alkyl, CF<sub>3</sub>, R<sub>12</sub>CO<sub>2</sub>, R<sub>12</sub>CO, R<sub>12</sub>CONH, etc.; R<sub>1</sub>R<sub>2</sub>, R<sub>2</sub>R<sub>3</sub>, R<sub>3</sub>R<sub>4</sub> = SCH<sub>2</sub>S, SCH<sub>2</sub>O, OCH<sub>2</sub>CH<sub>2</sub>S, etc.; R<sub>5</sub>, R<sub>6</sub> = H, alkyl, alkenyl, cycloalkyl, (substituted) Ph; R<sub>5</sub>R<sub>6</sub> = cycloalkyl; R<sub>7</sub> = H, alkyl, alkenyl, cycloalkyl, R<sub>13</sub>R<sub>14</sub>NCO, R<sub>13</sub>R<sub>14</sub>NCS, etc.; R<sub>6</sub>R<sub>7</sub> = (CH<sub>2</sub>)mCHR<sub>13</sub>NCO, (CH<sub>2</sub>)mCH<sub>2</sub>O<sub>2</sub>C, etc.; R<sub>8</sub>, R<sub>9</sub> = H, R<sub>13</sub>R<sub>14</sub>N, R<sub>12</sub>CONH, etc.; R<sub>10</sub> = H, halo, OH, R<sub>10</sub>, R<sub>13</sub>R<sub>14</sub>N, alkyl, CF<sub>3</sub>, R<sub>12</sub>CO<sub>2</sub>, etc.; R<sub>12</sub> = H, alkyl; R<sub>13</sub>, R<sub>14</sub> = H, alkyl, perfluoroalkyl, alkenyl, cycloalkyl; R<sub>13</sub>R<sub>14</sub> =

cycloalkyl; m = 0-2], were prepd. as kainate and/or AMPA antagonists (no data). Thus, 4-(4-acetylaminophenyl)-1,2-dihydro-1-methyl-6-methylthiophthalazine in CHCl<sub>3</sub> was treated with EtNCO to give 50% 4-(4-acetylaminophenyl)-1,2-dihydro-1-methyl-2-ethylcarbamoyl-6-methylthiophthalazine.

L67 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:796211 CAPLUS  
TITLE: Novel sulfur containing dihydrophthalazine antagonists of AMPA receptors  
AUTHOR(S): Li, Baoqing; Pei, Xue-Feng; Maccacchini, Maria  
CORPORATE SOURCE: Department of Medicinal Chemistry, Annovis, Inc, Aston, PA, 19014, USA  
SOURCE: Abstracts of Papers American Chemical Society (2000), 220th, MEDI-212  
CODEN: ACSRAL; ISSN: 0065-7727  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal; Meeting Abstract  
LANGUAGE: English

AB Excitatory neuronal transmission within the central nervous system is mediated predominately by ion flux through ion channels gated by glutamate. There are three major glutamate receptor subtypes: the N-methyl-D-aspartate (NMDA), 2S-amino-3-(5'-methyl-3'-hydroxyisoxazoline)-propionic acid (AMPA), and kainic acid (KA) receptor. Compds. that inhibit AMPA receptors have been shown to be effective neuroprotectants and have potential to treat epilepsy. We disclosed a series of promising dihydrophthalazines (DHP's) as non-competitive AMPA antagonists. We now report synthesis of novel sulfur contg. DHP's analogs. Structure-activity correlation of these novel analogs and other DHP's reveal the important contribution of the sulfur-based substituents in this class of noncompetitive inhibitors.

L67 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5

ACCESSION NUMBER: 1993:5264 BIOSIS  
DOCUMENT NUMBER: PREV199395005264  
TITLE: Noncompetitive inhibition of N-methyl-D-aspartate by conantokin G: Evidence for an allosteric interaction at polyamine sites.  
AUTHOR(S): Skolnick, Phil (1); Boje, Kathleen; Miller, Rachel; Pennington, Micheal; Maccacchini, Maria-Luisa  
CORPORATE SOURCE: (1) Lab. of Neuroscience, NIDDK/LN, NIH, Build. 8, Room 111, Bethesda, MD 20892 USA  
SOURCE: Journal of Neurochemistry, (1992) Vol. 59, No. 4, pp. 1516-1521.  
ISSN: 0022-3042.  
DOCUMENT TYPE: Article  
LANGUAGE: English

AB Conantokins T and G are polypeptide toxins present in snails of the genus Conus. These substances were recently reported to act as N-methyl-D-aspartate (NMDA) antagonists. In the present study, we examined the possible mechanisms producing this antagonism. Conantokin-G in inhibited spermine- and spermidine-stimulated (3H)MK-801 binding to extensively washed rat forebrain membranes in a noncompetitive manner with IC-50 values of apprx 4507 and apprx 946 nM, respectively. In contrast, **glutamate**-enhanced (3H)MK-801 binding was unaffected by conantokin-G concentrations of ltoreq 20 mu-M. At concentrations gtoreq 5 mu-M, conantokin-G effected a modest, noncompetitive inhibition of glycine-stimulated (3H)MK-801 binding and also produced a small enhancement of basal (3H)MK-801 binding. Conantokin-G reduced (IC-50 apprx 1.08 mu-M) the NMDA-stimulated accumulation of cyclic GMP in cerebellar granule cell cultures to basal values, but did not affect kainate-mediated

increases in cyclic GMP. These findings indicate that conantokin-G acts as a noncompetitive NMDA antagonist through an allosteric inhibition of polyamine responses. The neurochemical profile of this polypeptide is distinct from previously described noncompetitive NMDA antagonists.

L67 ANSWER 11 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:38485 BIOSIS

DOCUMENT NUMBER: PREV200200038485

TITLE: Increased expression of kainate receptors in mouse trisomy 16 cortical neurons: A model of Down syndrome.

AUTHOR(S): KlineBurgess, A. (1); Balbo, A.; Maccacchini, M. L.; Rapoport, S. I.; Galdzicki, Z. (1)

CORPORATE SOURCE: (1) Anatomy, Physiology and Genetic, Medical School, USUHS, Bethesda, MD USA

SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2344. print.

Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001

ISSN: 0190-5295.

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Ionotropic **glutamate** receptor interactions play a role in neuronal plasticity and neurodevelopment. Trisomy 16 mice (Ts16 and Ts65Dn) are considered models of Down syndrome (human trisomy 21), as the murine chromosome (Chr.) 16 is homologous to the long arm of human Chr. 21. The GluR5 subunit of the kainate (KA) subtype of **glutamate** receptors is coded by a gene localized on human Chr. 21 and mouse Chr. 16. We investigated the expression of the KA receptors using binding and Western blot techniques. Binding of (3H)-(2S,4R)-4-methylglutamate (SYM 2081), a novel KA receptor specific ligand, was quantified in trisomic and diploid mouse fetal cultured cortical neurons and in adult mouse cortical tissue. Fetal Ts16 and diploid neurons were maintained in serum-free Neurobasal/B27 medium for 10-14 days. Binding of (3H)SYM 2081 to the cultured neurons was measured by methods described (Galdzicki et al 1998). Cortical membranes were prepared using Ts65Dn and diploid brains (Toms et al. 1997). Non-specific binding was defined using 1 mM L-**glutamate**. (3H)SYM2081 (1 to 1000 nM) bound in a dose-dependent manner to cortical neurons in cultures and to the cortical membranes preparation. 100  $\mu$ M KA and 10  $\mu$ M domoate displaced almost 100% of 5 and 25 nM (3H)SYM2081 binding. 100  $\mu$ M ATPA (GluR5 specific antagonist) blocked 50% of specific binding. Ts16 cortical neurons and Ts65Dn cortical membranes showed approx 120% and 50% increases in specific binding, respectively. These results indicate an increased expression of KA receptors in trisomy 16 neurons, due to a gene-dosage effect.

L67 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:461674 BIOSIS

DOCUMENT NUMBER: PREV200000461674

TITLE: Novel sulfur containing dihydrophthalazine antagonists of AMPA receptors.

AUTHOR(S): Li, Baoqing (1); Pei, Xue-Feng (1); Maccacchini, Maria (1)

CORPORATE SOURCE: (1) Department of Medicinal Chemistry, Annovis, Inc, 34 Mt. Pleasant Dr, Aston, PA, 19014 USA

SOURCE: Abstracts of Papers American Chemical Society, (2000) Vol. 220, No. Part 1, pp. MEDI 212. print.

Meeting Info.: 220th National Meeting of the American Chemical Society Washington DC, Washington DC, USA August 20-24, 2000 American Chemical Society

. ISSN: 0065-7727.

DOCUMENT TYPE: Conference

LANGUAGE: English



SUMMARY LANGUAGE: English

L67 ANSWER 13 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:80874 BIOSIS

DOCUMENT NUMBER: PREV200100080874

TITLE: Dihydrophthalazines are novel allosteric antagonists of AMPA receptors in hippocampal neurons.

AUTHOR(S): Galdzicki, Z. (1); Pei, X. F.; Maccacchini, M. L.; Rapoport, S. I.; Howe, J. R.

CORPORATE SOURCE: (1) USUHS, Bethesda, MD USA

SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-339.9. print.

Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000  
Society for Neuroscience  
. ISSN: 0190-5295.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Excessive activation of AMPA receptors is thought to contribute importantly to excitotoxic injury. To develop new AMPA-receptor antagonists, we have synthesized a novel series of 1,2-dihydrophthalazines. Previous studies have shown that analogs from this series (SYM 2206, SYM 2189, SYM 2229) are effective AMPA receptors antagonists in cerebellar granule cells (Pei et al. 1999) and in spinal cord neurons (Irizarry et al. 1999). Since these compounds may have potential antiepileptic activity, we tested their effectiveness in hippocampal neurons. Whole-cell patch-clamp recordings were made from neurons in primary cultures of mouse embryonic hippocampus. In these neurons, kainate (KA) evoked sustained AMPA-receptor-mediated currents. These KA-evoked currents were blocked by each analog tested. Mean ( $\pm$  SEM) IC50 values were  $3 \pm 0.2$ ,  $10 \pm 2$  and  $26 \pm 7$   $\mu$ M for SYM 2229, SYM 2206 and SYM 2189, respectively (n=5-8 cells). Dihydrophthalazine block of KA-evoked currents was noncompetitive, but was independent of voltage and did not require channel opening. NMDA-evoked responses in the same neurons were unaltered. In contrast to the 2,3-benzodiazepines (e.g. GYKI 53655), AMPA-receptor inhibition by the dihydrothalazines is largely unaffected by cyclothiazide (100  $\mu$ M). We also found that SYM 2229 (30  $\mu$ M) blocked spontaneous miniature synaptic currents in a reversible fashion. These results show that the dihydrophthalazines are effective and selective allosteric AMPA receptor antagonists in hippocampal cultured neurons.

